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The evolving landscape of stroke prevention in atrial fibrillation within the United Kingdom between 2012 and 2016

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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 non-valvular atrial fibrillation (NVAF) and eligible for anticoagulation (CHA2DS2-VASc score ≥ 2) on 1st 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.

STRENGTHS AND LIMITATIONS

- A large representative population of patients with all forms of AF (paroxysmal, chronic) studied in the 'real-world' using data obtainted from GP 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 auditied 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 AC prescriptions is secondary care

Key words: Atrial Fibrillation, Drug Therapy, Electronic Health Records, Great Britain, Stroke

INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia,[1] estimated to affect up to 1.4 million people in England,[2] and is an independent risk factor for stroke, increasing the risk five-fold.[3]

Approximately 20% of stroke cases in the United Kingdom (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.[4, 5] However, AF-related strokes can be prevented and their impact minimised by effective management strategies including increased detection of AF, adherence to stroke prevention guidelines and anticoagulant (AC) use in at-risk patients.

Although anticoagulation is effective in preventing strokes due to AF, evidence suggests anticoagulation therapy remains underused.[6-12] In 2010, Holt et al. 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.[8] 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.[13] This update included three major changes based on new or strengthened evidence. Firstly, the CHA2DS2-VASc score replaced the CHADS2 score for the assessment of stroke risk. This is based on the accumulated evidence that CHA2DS2-VASc score, which is inclusive of the most common risk factors for stroke[14] and has been validated in multiple cohorts,[15] is better at identifying patients at “truly low risk” of AF-related stroke.[16-19] Secondly, the use of aspirin therapy for stroke prevention in AF was restricted to those patients who refuse oral anticoagulation. Thirdly, the use of non-vitamin K antagonist oral anticoagulants [(NOACs), such as dabigatran, apixaban, and rivaroxaban)] was recommended in preference to vitamin K antagonists (VKAs) in most patients with a CHA2DS2-VASc score ≥1.[13]

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.[20]

In 2014, when the National Institute for Health and Care Excellence (NICE) updated its AF clinical guidelines (CG180),[21] 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.[22]

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).[23] 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 (i.e., 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 (e.g., smoking status, 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 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[13] and NICE 2014[21] guidance at index date (CHA2DS2-VASc score ≥2) were included in five cross-sectional analyses: on 1st April of 2012, 2013, 2014, and 2015 and 1st 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 (e.g., 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 vitamin K antagonists, apixaban, rivaroxaban, dabigatran, and parenteral AC. International normalised ratio (INR) measurements were treated as an indicator of VKA exposure and was therefore 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.

Demographic characteristics included age, gender, and country of residence. Clinical characteristics were body mass index (BMI), 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 antiplatelet or nonsteroidal 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). CHA_2DS_2-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 READ 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% confidence interval were calculated 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 (FPFC = √(1-0.08) ~0.96).

An interrupted time series analysis [24] was conducted to estimate the impact of the updated ESC guidance (published in August 2012) and NICE 2014 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 (i.e., the rapid drop in rates immediately after the intervention) and trend (i.e., 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 anticoagulation management over time were also run separately in newly diagnosed patients with NVAF (<12 months) and in patients with NVAF with a diagnosis for ≥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 (GEE) were used to identify demographic and clinical characteristics associated withantiplatelet treatment , and with the absence of AT treatment (versus receiving anticoagulation therapy) 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 odds ratios and 95% confidence intervals. All analyses were conducted using SAS software version 9.4.

RESULTS

Patient Characteristics

The demographic and clinical characteristics of patients with NVAF eligible for anticoagulation according to ESC and NICE guidance (CHA2DS2-VASc ≥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 ≥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 ≥ 12 months). Similarly, the increase in the proportion of patients being prescribed AC was greater in those patients who were newly diagnosed compared to those diagnosed with NVAF for ≥ 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 ≥ 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, 21.5% rivaroxaban). No major change was observed in the NVAF population with a diagnosis for ≥ 12 months; VKA prescribed in 50.9% of the population in January 2016 and NOACs in 15% (including 4.5% apixaban, 2.2% dabigatran, 8.3% rivaroxaban).

Impact of ESC and NICE Guidelines Publications on UK Practice

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

Equally, a significant trend for decreasing antiplatelet 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: β=-0.26, post-NICE: β=-0.10) and after NICE for patients diagnosed ≥ 12 months (post-ESC: β=-0.15, post-NICE: β=-0.21).

Characteritics Associated with the Absence of Anticoagulation Therapy in April 2015

Tables 3 and 4 present the results of the GEE models comparing demographic and clinical characteristics in patients receiving either an AP alone or no AT, versus those receiving AC treatment in April 2015. Even after adjusting on CHA2DS2-VASc score, females, patients aged <65 and ≥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, CHA2DS2-VASc was associated with the absence of AT treatment, patients with a score ≥3 were less likely to remain untreated than patients with a CHA2DS2-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 to Wales and Northern Ireland.

DISCUSSION

A pronounced shift in anticoagulation management of patients with NVAF was observed in the UK between April 2012 and January 2016, coinciding with the update of ESC[13] and NICE[21] 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 1994-2003,[6, 7] no significant changes were observed in the years 2007–2010 in patients with CHA2DS2-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 (QOF) of the NHS (National Health Service), which provided equal emphasis on AC and AP in stroke prevention in primary care at that time.[12]

The observed shift in treatment patterns in this study suggests a positive impact of both the ESC[13] and NICE[21] guidelines in driving changes in thrombopropylaxis strategy for NVAF patients 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 on GP'swho 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 longstanding 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 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 NOAC's (apixaban, rivaroxaban, 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[21] 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, no major changes in the type of AC received by patients with NVAF with a diagnosis ≥ 12 months was observed.

Although these data show that anticoagulation treatment patterns in NVAF have improved substantially over the last five years, rates of anticoagulation appear to lag behind those observed in contemporary European cohorts. For example, at the two-year follow up of the EORP-AF registry in 2015, 79.2% of AF patients were identified as receiving at least one oral AC (compared to 62.9% in 2015 in this study, Table 2).[25] Rates of NOAC use however appear more comparable, with 13.7% of patients in EORP-AF receiving at least one NOAC (compared to 10.9% in this study in 2015). Baseline

data from the European population of the 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.[26] These data are comparable to 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 GARFIELD-AF registry of patients with very recently diagnosed NVAF (<6 weeks), over the period from 2010/11 to 2014/15 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%), whilst AP monotherapy declined from 30.2% to 16.6%.[27] It is encouraging that our data up to January 2016 continue to show anticoagulation 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[21] relative to the ESC guidance in 2012.[13] Other factors may also be involved.

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 CHA2DS2-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 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[7, 11, 12, 28-32] and may be secondary to an overestimation of bleeding risk despite unequivocal evidence of the benefits of AC in the elderly.[33-36]

Our findings clearly illustrate the risk-treatment paradox previously reported in AF management [11] that patients at higher risk of stroke who more likely to benefit from AC therapy [35] 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.[37]

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.[7] Given that women with AF appear to lose their protection against sudden death including stroke,[38] and may even have a higher mortality than men,[39] 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.

STRENGTHS AND LIMITATIONS

This is a large study of a representative population of NVAF patients 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.[8, 40] 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.

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.[41] 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 CRPD, 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, albeit 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 anticoagulation.

CONTRIBUTORSHIP STATEMENT

LL, CL, DE and JH conceived and designed the study. LM, MP and SR undertook the analysis. LL, ML, ER, MP, LM, SR, CL, DE, and JH contributed to the interpretation of the data. LM and LL wrote the first draft and ML, ER, MP, SR, CL, DE, and JH critically revieved the draft and approved the final manuscript as submitted.

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COMPETING INTERESTS

MP, LM, and SR were employees of Evidera who were paid consultants to Bristol-Myers Squibb (BMS) in connection with conducting this study and with the development of this manuscript. JH received consultancy fees from BMS for the conduct of this study. DE, ER, and LL were BMS employees at the time of the research. ML is a fulltime employee of Pfizer.

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DATA SHARING

No additional data are available.

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FIGURE LEGENDS

Figure 1. Flowchart describing the sample used in each year

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 CHA2DS2-VASc ≥ 2 separately in newly diagnosed patients (A) and patients diagnosed since 12 months or more (B)

A) Newly diagnosed patients with NVAF

B) Patients with NVAF diagnosis since 12 months or more

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

A. Anticoagulation treatment

	Pre-ESC[1]			**Post-ESC[2]**			**Post-NICE[2]**		
	β	SE	p-value	β	SE	p-value	β	SE	p-value
Diagnosed < 12 months									
Level	43.09	0.26	<.0001	0.28	0.35	0.418	0.10	0.49	0.846
Trend	0.34	0.02	<.0001	0.26	0.03	<.0001	0.12	0.09	0.171
Diagnosed ≥ 12 months									
Level	49.01	0.07	<.0001	0.00	0.10	0.981	-0.16	0.14	0.251
Trend	0.13	0.01	<.0001	0.18	0.01	<.0001	0.15	0.02	<.0001

[1]For Pre-ESC data are base level, base trend. [2]Post-ESC and Post-NICE data are change in level, change in trend

B. Aspirin (ASA) or other AP only

	Pre-ESC[1]			Post-ESC[2]			Post-NICE[2]		
	β	SE	p-value	β	SE	p-value	β	SE	p-value
Diagnosed <12months									
Level	41.94	0.24	<.0001	-0.20	0.31	0.518	-0.63	0.44	0.159
Trend	-0.36	0.02	<.0001	-0.26	0.03	<.0001	-0.10	0.08	0.226
Diagnosed ≥12 months									
Level	35.05	0.06	<.0001	0.03	0.08	0.737	-0.33	0.12	0.008
Trend	-0.12	0.01	<.0001	-0.15	0.01	<.0001	-0.21	0.02	<.0001

[1]For Pre-ESC data are base level, base trend. [2]Post-ESC and Post-NICE data are change in level, change in trend

C. Without any antithrombotic treatment

	Pre-ESC[1]			Post-ESC[2]			Post-NICE[2]		
	β	SE	p-value	β	SE	p-value	β	SE	p-value
Diagnosed <12months									
Level	14.97	0.15	<.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 ≥12 months									
Level	15.94	0.07	<.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

[1]For Pre-ESC data are base level, base trend. [2]Post-ESC and Post-NICE data are change in level, change in trend

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

	April 2012 (n=67327)		April 2013 (n=66364)		April 2014 (n=62840)		April 2015 (n=53150)		Jan 2016 (n=45105)	
	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	51055	75.8	49721	74.9	45422	72.3	36910	69.4	28226	62.6
Wales	7193	10.7	7168	10.8	7658	12.2	6791	12.8	7088	15.7
Scotland	6826	10.1	7132	10.7	7331	11.7	6850	12.9	7060	15.7
Northern Ireland	2253	3.3	2343	3.5	2429	3.9	2599	4.9	2731	6.1
Smoking status										
Current smoker	4685	7.0	4500	6.8	4087	6.5	3305	6.2	2877	6.4
Past smoker	34297	50.9	34019	51.3	32258	51.3	27389	51.5	23119	51.3
Body mass index (kg/m^2)										
Missing data	5283	7.8	4588	6.9	3990	6.3	3209	6.0	2667	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	8197	12.2	8104	12.2	7421	11.8	6255	11.8	5564	12.3
Stroke risk factors										
Previous stroke/TIA	13136	19.5	12966	19.5	12312	19.6	10393	19.6	8986	19.9
Other arterial thromboembolism	281	0.4	267	0.4	243	0.4	207	0.4	182	0.4
Congestive heart failure	11970	17.8	11536	17.4	10780	17.2	9296	17.5	8272	18.3
Coronary artery disease	21158	31.4	20213	30.5	18691	29.7	15383	28.9	12892	28.6
Peripheral arterial disease	4136	6.1	3978	6	3671	5.8	2958	5.6	2491	5.5
Hypertension	65349	97.1	64557	97.3	61255	97.5	51872	97.6	44039	97.6
Diabetes mellitus	13949	20.7	13974	21.1	13564	21.6	11779	22.2	10222	22.7

	April 2012 (n=67327)		April 2013 (n=66364)		April 2014 (n=62840)		April 2015 (n=53150)		Jan 2016 (n=45105)	
	n	%	n	%	n	%	n	%	n	%
CHA2DS2-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 bleedings	22136	32.9	22260	33.5	21770	34.6	18669	35.1	15889	35.2
Intracranial	1166	1.7	1223	1.8	1238	2.0	1039	2.0	897	2.0
Gastrointestinal	7755	11.5	7700	11.6	7575	12.1	6536	12.3	5677	12.6
Renal disease	23367	34.7	23003	34.7	21391	34	17796	33.5	15061	33.4
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)	

Abbreviations: GP, general practitioner; NVAF, non-valvular atrial fibrillation; SD, standard deviation; TIA, transient ischaemic attack

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

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 ≥ 2

	April 2012 % (95% CI)	April 2013 % (95% CI)	April 2014 % (95% CI)	April 2015 % (95% CI)	January 2016 % (95% CI)
Anticoagulation	**50.2** (49.8-55.5)	**53.2** (52.8-53.5)	**57.5** (57.1-57.9)	**62.9** (62.5-63.3)	**66.9** (66.5-67.3)
Antiplatelet therapy alone	**34.2** (33.9-34.5)	**31.2** (30.8-31.5)	**27.7** (27.3-28.0)	**21.8** (21.5-22.2)	**17.4** (17.1-17.8)
No antithrombotic therapy	**15.6** (15.4-15.9)	**15.7** (15.4-15.9)	**14.8** (14.6-15.1)	**15.3** (15.0-15.6)	**15.7** (15.4-16.0)

Abbreviations: CI, confidence interval

Table 3. Factors associated with the prescription of aspirin or other antiplatelet for TE prevention in NVAF in April 2015 (vs. anticoagulation): results of the GEE model

	Antiplatelet therapy alone N=11,609		Treated with anticoagulant N= 33,413		OR (95% CI)	P-value
	n	%	N	%		
Patient age (years)						< .0001
< 65	890	7.7	2016	6.0	1.22 (1.10-1.35)	
65 to 74	2769	23.9	8780	26.3	Reference	
75 to 84	3842	33.1	14363	43.0	0.94 (0.87-1.02)	
≥ 85	4108	35.4	8254	24.7	1.72 (1.58-1.87)	
Country						0.001
England	8065	69.5	22909	68.6	Reference.	
Wales	1383	11.9	4524	13.5	0.80 (0.70-0.91)	
Scotland	1590	13.7	4231	12.7	1.06 (0.96-1.19)	
N. Ireland	571	4.9	1749	5.2	0.83 (0.72-0.97)	
Gender: male (reference = female)	5364	46.2	14580	43.6	0.87 (0.81-0.93)	<.0001
Time since NVAF diagnosis						<.0001
< 6 months	497	4.3	2121	6.3	Reference	
6 to 12 months	442	3.8	2175	6.5	0.96 (0.83-1.11)	
12 to 24 months	979	8.4	3886	11.6	1.24 (1.10-1.41)	
2 to 5 years since	3095	26.7	8496	25.4	1.89 (1.68-2.12)	
≥ 5 years	6596	56.8	16735	50.1	2.17 (1.93-2.44)	
Previous oral AC treatment						<.0001
No previous treatment	8093	69.7	21189	63.4	Reference	
NOAC only	87	0.7	411	1.2	0.61 (0.46-0.81)	
VKA and NOAC	76	0.7	490	1.5	0.37 (0.29-0.47)	
VKA only	3353	28.9	11323	33.9	0.65 (0.59-0.72)	
Previous stroke/TIA/arterial TE	2291	19.7	7341	22.0	0.83 (0.75-0.92)	0.0008
Congestive heart failure	1722	14.8	6685	20.0	0.61 (0.56-0.66)	<.0001
Previous coronary artery disease	4535	39.1	9636	28.8	1.60 (1.50--1.71)	<.0001

	Antiplatelet therapy alone N=11,609		Treated with anticoagulant N= 33,413		OR (95% CI)	P-value
	n	%	N	%		
Peripheral arterial disease	833	7.2	1887	5.6	1.20 (1.10-1.31)	0.0001
Hypertension	11308	97.4	32869	98.4	0.59 (0.51-0.69)	<.0001
CHA2DS2-VASc score						<.0001
2	1425	12.3	3444	10.3	Reference	
3	2408	20.7	7482	22.4	0.69 (0.63-0.76)	
4	3206	27.6	9656	28.9	0.56 (0.50-0.64)	
5	2306	19.9	6544	19.6	0.54 (0.46-0.64)	
≥6	2264	19.5	6287	18.9	0.52 (0.42-0.65)	
Previous bleed						<.0001
No bleed	7522	64.8	21577	64.6	Reference	
Intracranial bleed	346	3.0	404	1.2	3.02 (2.56-3.56)	
Gastrointestinal bleed	1430	12.3	4001	11.8	0.96 (0.90-1.02)	
Other bleed	2311	19.9	7473	22.4	0.82 (0.77-0.87)	
History of fall	3474	29.9	8211	24.6	1.14 (1.08-1.20)	<.0001
Renal disease	4106	35.4	11542	34.5	0.94 (0.90-0.99)	0.0131
Liver disease	102	0.9	214	0.6	1.32 (1.03-1.70)	0.0414
Number of comedications						<.0001
< 5	1448	12.5	6879	20.6	Reference	
5 to 9	5040	43.4	14825	44.4	1.71 (1.60-1.82)	
10 to 14	3169	27.3	7782	23.3	2.08 (1.93-2.26)	
15 or more	1952	16.8	3927	11.8	2.66 (2.43-2.91)	

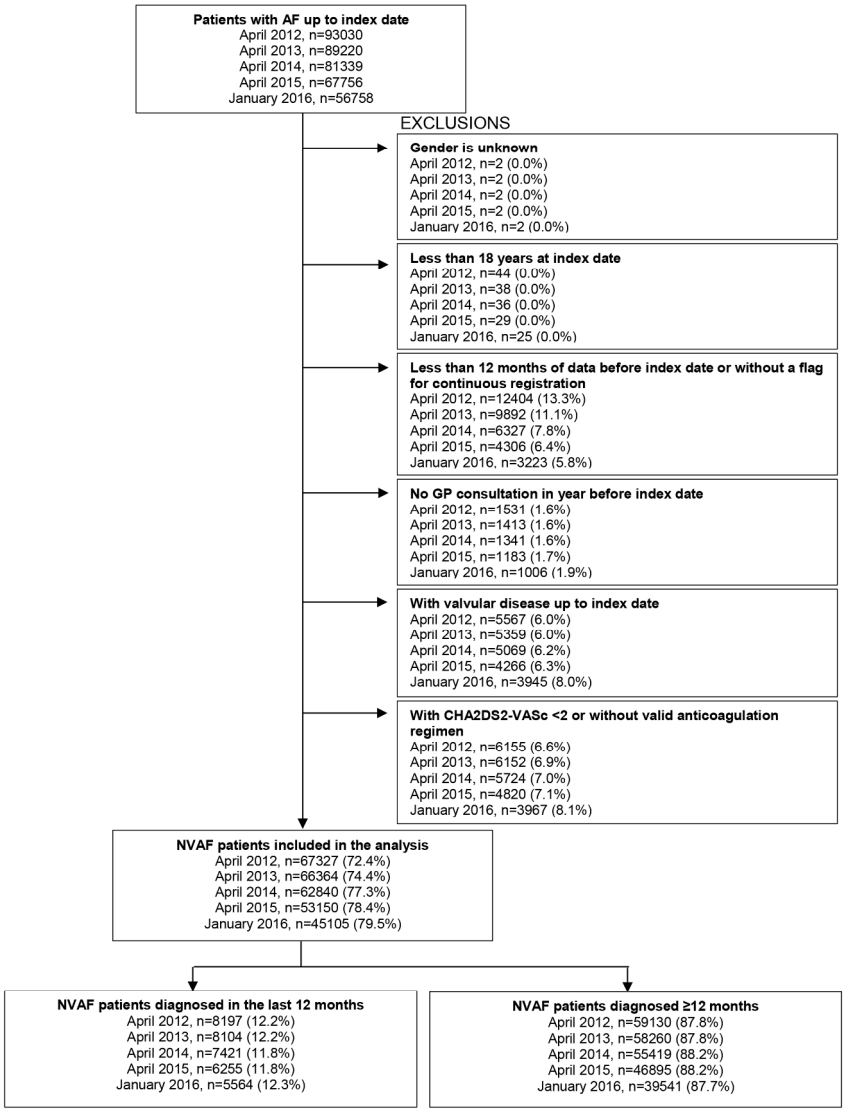
Abbreviations: CI, confidence interval; GEE, generalised estimating equations; VKA, vitamin K antagonist; OAC, oral anticoagulant; NVAF, non-valvular atrial fibrillation; TIA, transient ischaemic attack; TE, thromboembolism; OR, odds ratio; NOAC, novel oral anticoagulant.

Table 4. 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=8,128		Treated with anticoagulant N= 33,413		OR (95% CI)	P-value
	n	%	n	%		
Patient age (years)						<.0001
< 65	1299	16	2016	6.0	1.64 (1.47-1.83)	
65 to 74	2214	27.2	8780	26.3	Reference	
75 to 84	2367	29.1	14363	43.0	1.09 (0.99-1.20)	
≥ 85	2248	27.7	8254	24.7	1.86 (1.68-2.07)	
Gender: male (reference = female)	4450	54.7	14580	43.6	0.51 (0.46-0.56)	<.0001
Country						
England	5936	73.0	22909	68.6	Reference	<.0001
Wales	884	10.9	4524	13.5	0.80 (0.69-0.93)	
Scotland	1029	12.7	4231	12.7	1.09 (0.96-1.23)	
Northern Ireland	279	3.4	1749	5.2	0.69 (0.57-0.83)	
Time since NVAF diagnosis						<.0001
< 6 months	592	7.3	2121	6.3	Reference	
6 to 12 months	427	5.3	2175	6.5	0.71 (0.61-0.82)	
12 to 24 months	864	10.6	3886	11.6	0.82 (0.71-0.94)	
2 to 5 years	2086	25.7	8496	25.4	0.93 (0.82-1.06)	
≥ 5 years	4159	51.2	16735	50.1	1.07 (0.94-1.23)	
Previous OAC treatment						<.0001
No previous OAC	5137	63.2	21189	63.4	Reference	
NOAC only	189	2.3	411	1.2	1.82 (1.36-2.43)	
VKA and NOAC	159	2.0	490	1.5	1.50 (1.23-1.84)	
VKA only	2643	32.5	11323	33.9	0.97 (0.88-1.07)	
Previous stroke/TIA/ arterial TE	968	11.9	7341	22.0	0.55 (0.48-0.64)	<.0001
Congestive heart failure	889	10.9	6685	20.0	0.76 (0.69-0.84)	<.0001

Parameter	No antithrombotic therapy N=8,128		Treated with anticoagulant N= 33,413		OR (95% CI)	P-value
	n	%	n	%		
Previous coronary artery disease	1212	14.9	9636	28.8	0.76 (0.70-0.84)	<.0001
Hypertension	7695	94.7	32869	98.4	0.62 (0.53-0.72)	<.0001
CHA2DS2-VASc score						<.0001
2	2212	27.2	3444	10.3	Reference	
3	2034	25	7482	22.4	0.48 (0.43-0.54)	
4	2057	25.3	9656	28.9	0.33 (0.28-0.39)	
5	987	12.1	6544	19.6	0.28 (0.22-0.35)	
≥6	838	10.27	6287	18.9	0.27 (0.20-0.36)	
Previous bleed						<.0001
No bleed	5382	66.2	21577	64.6	Reference	
IC bleed	289	3.6	404	1.2	8.03 (6.43-10.02)	
GI bleed	1016	12.5	4001	11.8	1.24 (1.14-1.35)	
Other bleed	1441	17.7	7473	22.4	0.91 (0.85-0.97)	
History of peptic ulcer	465	5.7	1743	5.2	1.36 (1.21-1.52)	<.0001
History of anaemia	227	2.8	880	2.6	1.44 (1.24-1.67)	<.0001
History of fall	2097	25.8	8211	24.6	1.20 (1.13-1.28)	<.0001
Renal disease	2148	26.4	11542	34.5	0.90 (0.84-0.96)	0.0016
Liver disease	109	1.3	214	0.6	2.39 (1.87-3.05)	<.0001
Active cancer	455	3.9	1367	4.1	1.19 (1.06-1.35)	0.0053
Number of co-medications						<.0001
< 5	3384	41.6	6879	20.6	Reference	
5 to 9	2791	34.3	14825	44.4	0.49 (0.45-0.52)	
10 to 14	1271	15.6	7782	23.3	0.46 (0.43-0.50)	
≥15	682	8.4	3927	11.8	0.53 (0.48-0.59)	

Abbreviations: CI, confidence interval; GEE, generalised estimating equations; VKA, vitamin K antagonist; OAC, oral anticoagulant; NVAF, non-valvular atrial fibrillation; TIA, transient ischaemic attack; TE, thromboembolism; OR, odds ratio; NOAC, novel oral anticoagulant



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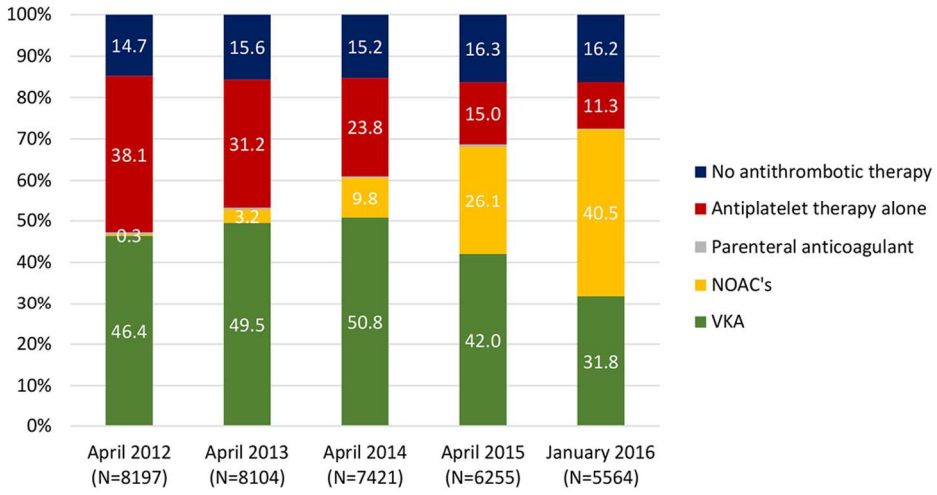

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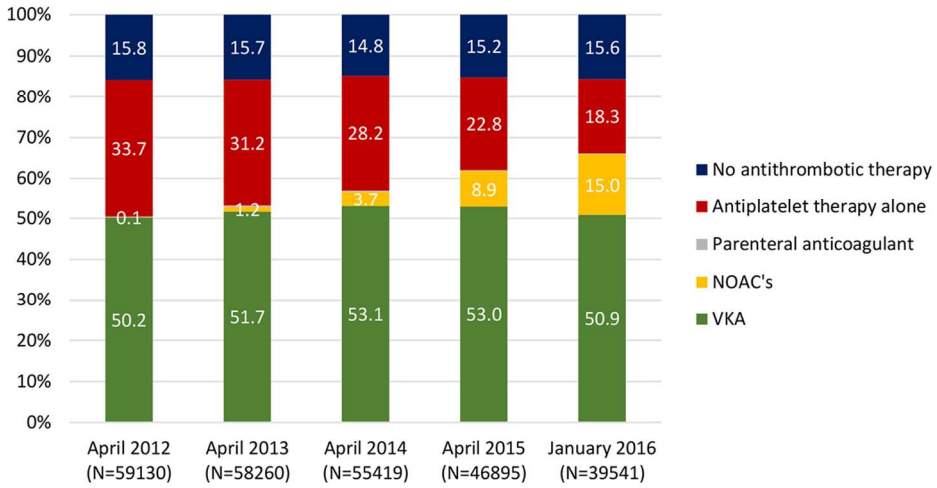

FIgure 2

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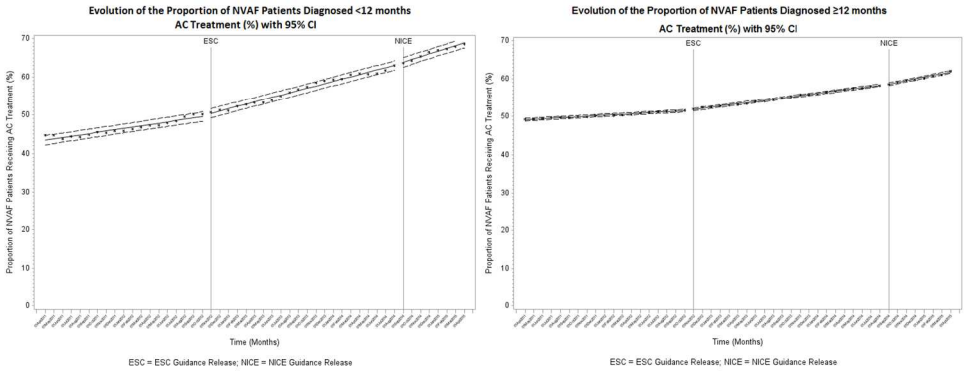
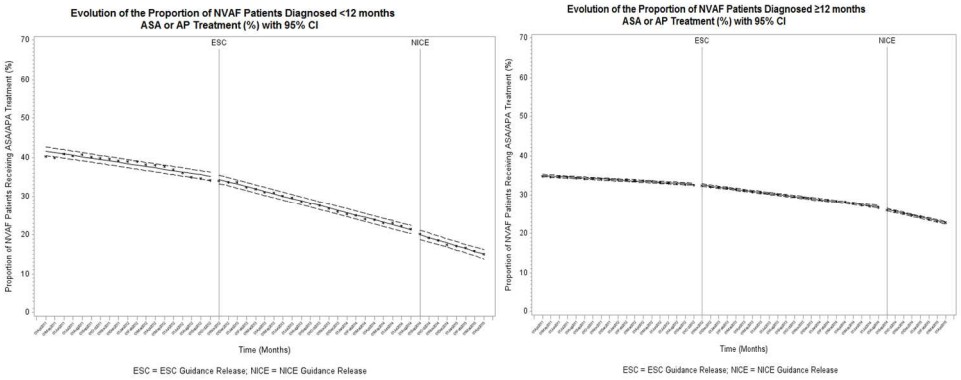
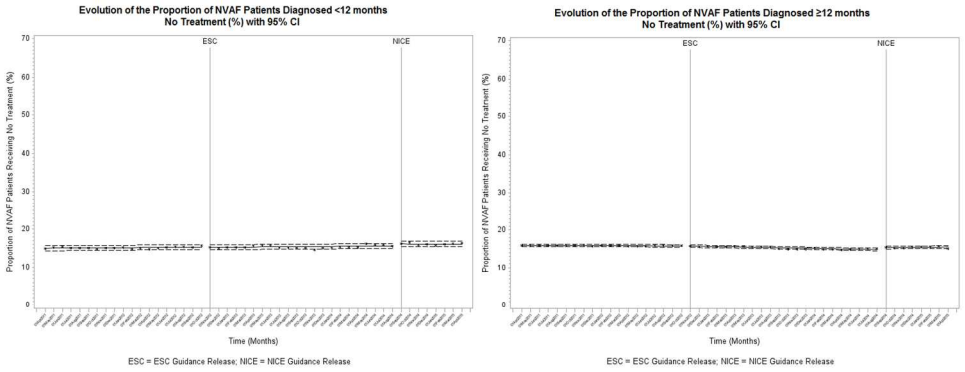


172x68mm (300 x 300 DPI)



172x70mm (300 x 300 DPI)



172x70mm (300 x 300 DPI)

DATA SUPPLEMENT

Table s1. READ code descriptions

G11..00	Mitral valve diseases
G540.15	Mitral valve prolapse
G110.00	Mitral stenosis
G540.00	Mitral valve incompetence
G541.00	Aortic valve disorders
G540000	Mitral incompetence, non-rheumatic
G130.00	Mitral and aortic stenosis
G13..00	Diseases of mitral and aortic valves
G541400	Aortic valve stenosis with insufficiency
G131.14	Mitral stenosis and aortic regurgitation
G544200	Combined disorders of mitral, aortic and tricuspid valves
G541z00	Aortic valve disorders NOS
G544100	Disorders of both mitral and tricuspid valves
G540z00	Mitral valve disorders NOS
G113.00	Nonrheumatic mitral valve stenosis
G13z.00	Mitral and aortic valve disease NOS
G11z.00	Mitral valve disease NOS
G133.00	Mitral and aortic incompetence
G132.12	Mitral incompetence and aortic stenosis
G540200	Mitral valve prolapse
G132.00	Mitral insufficiency and aortic stenosis
G132.13	Mitral regurgitation and aortic stenosis
G540100	Mitral incompetence, cause unspecified
G540300	Mitral valve leaf prolapse
G544.00	Multiple valve diseases
G540.12	Mitral valve insufficiency
G112.13	Mitral stenosis with regurgitation
G112.00	Mitral stenosis with insufficiency
Gyu5600	[X]Other aortic valve disorders
G131.00	Mitral stenosis and aortic insufficiency
G12z.00	Rheumatic aortic valve disease NOS
G112.12	Mitral stenosis with incompetence
Gyu1000	[X]Other mitral valve diseases
P65..00	Congenital mitral stenosis

Management of NVAF in Europe and the UK

G544X00	Multiple valve disease, unspecified
G114.00	Ruptured mitral valve cusp
G131.13	Mitral stenosis and aortic incompetence
P66..00	Congenital mitral insufficiency
P652.00	Parachute deformity of the mitral valve
G13y.00	Multiple mitral and aortic valve involvement
Gyu5A00	[X]Aortic valve disorders in diseases classified elsewhere
P650.00	Congenital mitral stenosis, unspecified
G133.11	Mitral and aortic insufficiency
Gyu5500	[X]Other nonrheumatic mitral valve disorders
P65z.00	Congenital mitral stenosis NOS
Gyu5D00	[X]Multiple valve disorders/diseases CE
READ Codes for prosthetic valve description	
7911.12	Replacement of aortic valve
P641.00	Bicuspid aortic valve
7910300	Replacement of mitral valve NEC
7910.12	Replacement of mitral valve
7910.12	Replacement of mitral valve
7914300	Replacement of valve of heart NEC
7914200	Prosthetic replacement of valve of heart NEC
7910.00	Plastic repair of mitral valve
7911.00	Plastic repair of aortic valve
7911300	Replacement of aortic valve NEC
7915000	Revision of plastic repair of mitral valve
7916000	Open mitral valvotomy
7917000	Closed mitral valvotomy
7910200	Prosthetic replacement of mitral valve
7910200	Prosthetic replacement of mitral valve
7910400	Mitral valvuloplasty NEC
ZV43300	[V]Has artificial heart valve
7914.11	Replacement of unspecified valve of heart
7910211	Bjork-Shiley prosthetic replacement of mitral valve
7911200	Prosthetic replacement of aortic valve
7910.11	Mitral valvuloplasty
7914212	Starr prosthetic replacement of valve of heart
7911100	Xenograft replacement of aortic valve

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7911y00	Other specified plastic repair of aortic valve
ZV45H00	[V]Presence of prosthetic heart valve
7910z00	Plastic repair of mitral valve NOS
7911000	Allograft replacement of aortic valve
7915100	Revision of plastic repair of aortic valve
7914211	Edwards prosthetic replacement of valve of heart
TB01200	Implant of heart valve prosthesis + complication, no blame
7910213	Carpentier prosthetic replacement of mitral valve
7910100	Xenograft replacement of mitral valve
7919000	Percutaneous transluminal mitral valvotomy
7911z00	Plastic repair of aortic valve NOS
7910212	Bjork-Shiley prosthetic replacement of mitral valve
7910y00	Other specified plastic repair of mitral valve
SP00200	Mechanical complication of heart valve prosthesis
SyuK611	[X] Embolism from prosthetic heart valve
790D700	Replacement of valved cardiac conduit
7914100	Xenograft replacement of valve of heart NEC
7914000	Allograft replacement of valve of heart NEC
ZVu6e00	[X]Presence of other heart valve replacement
7910214	Edwards prosthetic replacement of mitral valve
7910411	Mitral valve repair NEC
7911411	Aortic valve repair NEC
7910000	Allograft replacement of mitral valve
7911600	Transluminal aortic valve implantation
7911500	Transapical aortic valve implantation
7914600	Replacement of truncal valve
7918000	Annuloplasty of mitral valve

Table s2. Proportion of patients with NVAF treated in April 2012, 2013, 2014, and 2015 in the UK, according to duration of diagnosis

	April 2012 % [95% CI]	April 2013 % [95% CI]	April 2014 % [95% CI]	April 2015 % [95% CI]	January 2016 % [95% CI]
Diagnosed < 12 months					
Anticoagulation treatment	**47.2 [46.2-48.3]**	**53.2 [52.1-54.2]**	**61.0 [59.9-62.0]**	**68.7 [67.6-69.8]**	**72.5 [71.3-73.7]**
VKA	46.4 [45.4-47.4]	49.5 [48.5-50.6]	50.8 [49.7-51.9]	42.0 [40.8-43.1]	31.8 [30.6-33.0]
Apixaban	-	-	1.7 [1.5-2.0]	8.8 [8.1-9.5]	16.6 [15.6-17.5]
Rivaroxaban	-	1.2 [1.0-1.5]	5.5 [5.0-6.0]	14.5 [13.7-15.3]	21.5 [20.4-22.6]
Dabigatran	0.3 [0.2-0.4]	2.0 [1.7-2.3]	2.6 [2.3-2.9]	2.8 [2.5-3.2]	2.4 [2.0-2.8]
Parenteral anticoagulant	0.5 [0.4-0.6]	0.5 [0.3-0.6]	0.4 [0.2-0.5]	0.6 [0.4-0.8]	0.2 [0.1-0.4]
Antiplatelet therapy alone	**38.1 [37-39.1]**	**31.2 [30.2-32.1]**	**23.8 [22.9-24.8]**	**15 [14.2-15.9]**	**11.3 [10.5-12.1]**
No antithrombotic therapy	**14.7 [14-15.4]**	**15.6 [14.9-16.4]**	**15.2 [14.4-16]**	**16.3 [15.4-17.2]**	**16.2 [15.2-17.1]**
Diagnosed ≥ 12 months					
Anticoagulation treatment	**50.6 [50.2-51.0]**	**53.2 [52.8-53.5]**	**57.0 [56.6-57.4]**	**62.1 [61.7-62.5]**	**66.1 [65.6-66.6]**
VKA	50.2 [49.8-50.6]	51.7 [51.3-52.1]	53.1 [52.7-53.5]	53.0 [52.5-53.4]	50.9 [50.4-51.4]
Apixaban	-	-	0.4 [0.3-0.4]	2.0 [1.9-2.1]	4.5 [4.3-4.7]
Rivaroxaban	-	0.5 [0.4-0.5]	1.9 [1.8-2.0]	4.9 [4.7-5.1]	8.3 [8.0-8.6]
Dabigatran	0.1 [0.1-0.1]	0.7 [0.7-0.8]	1.4 [1.3-1.5]	2.0 [1.9-2.1]	2.2 [2.1-2.4]
Parenteral anticoagulant	0.2 [0.2-0.3]	0.3 [0.2-0.3]	0.3 [0.2-0.3]	0.2 [0.2-0.3]	0.2 [0.2-0.3]
Antiplatelet therapy alone	**33.7 [33.3-34.0]**	**31.2 [30.8-31.5]**	**28.2 [27.8-28.5]**	**22.8 [22.4-23.1]**	**18.3 [17.9-18.7]**
No antithrombotic therapy	**15.8 [15.5-16.0]**	**15.7 [15.4-16.0]**	**14.8 [14.5-15.1]**	**15.2 [14.8-15.5]**	**15.6 [15.3-16.0]**

Abbreviations: CI, confidence interval; VKA, vitamin K antagonists

Table s3. Proportion of patients with NVAF treated in April 2012, 2013, 2014, and 2015 in the UK,. according to country of residence

	April 2012 % [95% CI]	April 2013 % [95% CI]	April 2014 % [95% CI]	April 2015 % [95% CI]	January 2016 % [95% CI]
England					
Anticoagulation treatment	**49.6 [49.2-50]**	**52.4 [52-52.9]**	**56.9 [56.5-57.4]**	**62.1 [61.6-62.5]**	**66.5 [66.0-67.1]**
VKA	49.2 [48.8-49.6]	50.8 [50.4-51.2]	52.4 [51.9-52.8]	51.3 [50.8-51.8]	47.9 [47.4-48.5]
Apixaban	-	-	0.4 [0.4-0.5]	2.3 [2.2-2.5]	5.0 [4.8-5.3]
Rivaroxaban	-	0.5 [0.4-0.5]	2.1 [2.0-2.2]	5.7 [5.5-5.9]	10.7 [10.3-11.0]
Dabigatran	0.1 [0.1-0.1]	0.9 [0.8-1.0]	1.7 [1.6-1.8]	2.4 [2.3-2.6]	2.6 [2.4-2.8]
Parenteral anticoagulant	0.3 [0.2-0.3]	0.3 [0.2-0.3]	0.3 [0.3-0.4]	0.3 [0.3-0.4]	0.2 [0.2-0.3]
Antiplatelet therapy alone	**33.9 [33.5-34.3]**	**30.9 [30.6-31.3]**	**27.5 [27.1-27.9]**	**21.9 [21.4-22.3]**	**17.0 [16.5-17.4]**
No antithrombotic therapy	**16.5 [16.2-16.8]**	**16.6 [16.3-16.9]**	**15.6 [15.3-15.9]**	**16.1 [15.7-16.4]**	**16.5 [16.1-17.0]**
Scotland					
Anticoagulation treatment	**48.8 [47.7-49.9]**	**51.9 [50.8-53]**	**55.5 [54.4-56.6]**	**61.8 [60.7-62.9]**	**64.3 [63.2-65.4]**
VKA	48.2 [47.1-49.3]	49.2 [48.1-50.3]	49.1 [48.0-50.2]	48.4 [47.2-49.5]	45.2 [44-46.3]
Apixaban	-	-	0.5 [0.3-0.6]	2.7 [2.3-3.0]	6.6 [6.0-7.2]
Rivaroxaban	-	1.8 [1.5-2.0]	5.0 [4.5-5.4]	9.8 [9.1-10.5]	11.6 [10.8-12.3]
Dabigatran	0.4 [0.2-0.5]	0.5 [0.4-0.7]	0.7 [0.5-0.8]	0.7 [0.5-0.8]	0.8 [0.6-1.0]
Parenteral anticoagulant	0.2 [0.1-0.3]	0.4 [0.2-0.5]	0.3 [0.2-0.4]	0.2 [0.1-0.3]	0.1 [0.1-0.2]
Antiplatelet therapy alone	**37 [35.9-38.1]**	**33.6 [32.6-34.7]**	**29.6 [28.6-30.6]**	**23.2 [22.3-24.2]**	**19.9 [19.0-20.8]**
No antithrombotic therapy	**14.2 [13.4-15.0]**	**14.5 [13.7-15.3]**	**14.9 [14.2-15.7]**	**15 [14.2-15.8]**	**15.8 [14.9-16.6]**
Wales					
Anticoagulation treatment	**55.1 [54.0-56.2]**	**58.7 [57.7-59.8]**	**61.7 [60.6-62.7]**	**66.6 [65.5-67.7]**	**69.1 [68.0-70.2]**
VKA	54.8 [53.7-55.9]	57.6 [56.5-58.7]	59.1 [58.0-60.1]	59.3 [58.1-60.4]	57.6 [56.5-58.8]
Apixaban	-	0.0 [0.0-0.1]	0.3 [0.2-0.4]	2.2 [1.9-2.5]	3.9 [3.4-4.3]
Rivaroxaban	-	0.1 [0.0-0.2]	0.9 [0.7-1.1]	3.2 [2.8-3.6]	5.1 [4.6-5.6]
Dabigatran	0.0 [0.0-0.1]	0.9 [0.6-1.1]	1.3 [1.1-1.5]	1.9 [1.6-2.2]	2.3 [2.0-2.7]
Parenteral anticoagulant	0.2 [0.1-0.3]	0.2 [0.1-0.3]	0.1 [0.1-0.2]	0.1 [0.0-0.1]	0.2 [0.1-0.2]
Antiplatelet therapy alone	**32.5 [31.5-33.6]**	**29.4 [28.4-30.4]**	**26.7 [25.8-27.7]**	**20.4 [19.4-21.3]**	**16.8 [15.9-17.7]**
No antithrombotic therapy	**12.4 [11.6-13.1]**	**11.9 [11.2-12.6]**	**11.6 [10.9-12.3]**	**13.0 [12.2-13.8]**	**14.1 [13.3-14.9]**
Northern Ireland					
Anticoagulation treatment	**51.5 [49.6-53.5]**	**55 [53.0-56.9]**	**60.8 [59.0-62.7]**	**67.3 [65.6-69.0]**	**71.9 [70.2-73.6]**
VKA	50.7 [48.7-52.7]	52.4 [50.4-54.3]	51.5 [49.6-53.4]	46 [44.2-47.9]	39.7 [37.9-41.6]
Apixaban	-	0.1 [0.0-0.2]	3.1 [2.4-3.7]	11.1 [10.0-12.3]	19.1 [17.6-20.6]
Rivaroxaban	-	0.4 [0.1-0.6]	3.5 [2.8-4.2]	7.5 [6.5-8.4]	10.7 [9.5-11.8]
Dabigatran	0.5 [0.2-0.8)	1.6 [1.1-2.1]	2.5 [1.9-3.1]	2.3 [1.8-2.9]	2.1 [1.6-2.7]

Management of NVAF in Europe and the UK

	April 2012 % [95% CI]	April 2013 % [95% CI]	April 2014 % [95% CI]	April 2015 % [95% CI]	January 2016 % [95% CI]
Parenteral anticoagulant	0.3 [0.1-0.5]	0.6 [0.3-0.8]	0.2 [0.1-0.4]	0.3 [0.1-0.6]	0.3 [0.1-0.5]
Antiplatelet therapy alone	**37.9 [35.9-39.8]**	**34.1 [32.2-35.9]**	**28.2 [26.4-29.9]**	**22 [20.4-23.5]**	**17.2 [15.8-18.6]**
No antithrombotic therapy	**10.6 [9.4-11.8]**	**11 [9.8-12.2]**	**11.0 [9.8-12.2]**	**10.7 [9.6-11.9]**	**10.9 [9.8-12.1]**

Abbreviations: CI, confidence interval; VKA, vitamin K antagonists

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any pre-specified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4-5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4-5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	n/a
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4-5
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	n/a
		(*c*) Explain how missing data were addressed	n/a
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	10
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	20
		(b) Give reasons for non-participation at each stage	20
		(c) Consider use of a flow diagram	20
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	16
		(b) Indicate number of participants with missing data for each variable of interest	16
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	n/a
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	n/a
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	n/a
		Cross-sectional study—Report numbers of outcome events or summary measures	6, 16, 17-19
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	17
		(*b*) Report category boundaries when continuous variables were categorized	18-19
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10
Discussion			
Key results	18	Summarise key results with reference to study objectives	8
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9-10
Generalisability	21	Discuss the generalisability (external validity) of the study results	10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

The evolving landscape of stroke prevention in atrial fibrillation within the United Kingdom between 2012 and 2016

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The evolving landscape of stroke prevention in atrial fibrillation within the United Kingdom between 2012 and 2016

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Short title: Evolving stroke prevention for NVAF in the UK

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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 non-valvular atrial fibrillation (NVAF) and eligible for anticoagulation (CHA2DS2-VASc score ≥ 2) on 1st 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.

STRENGTHS AND LIMITATIONS

- A large representative population of patients with all forms of AF (paroxysmal, chronic) studied in the 'real-world' using data obtainted from GP 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 auditied 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 AC prescriptions is secondary care

Key words: Atrial Fibrillation, Drug Therapy, Electronic Health Records, Great Britain, Stroke

INTRODUCTION

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

Approximately 20% of stroke cases in the United Kingdom (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.[5, 6] However, AF-related strokes can be prevented and their impact minimised by effective management strategies including increased detection of AF, adherence to stroke prevention guidelines and anticoagulant (AC) use in at-risk patients.

Although anticoagulation is effective in preventing strokes due to AF, evidence suggests anticoagulation therapy remains underused.[7-13] In 2010, Holt et al. 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.[9] 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.[14] This update included three major changes based on new or strengthened evidence. Firstly, the CHA2DS2-VASc score replaced the CHADS2 score for the assessment of stroke risk. This is based on the accumulated evidence that CHA2DS2-VASc score, which is inclusive of the most common risk factors for stroke[15] and has been validated in multiple cohorts,[16] is better at identifying patients at “truly low risk” of AF-related stroke.[17-20] Secondly, the use of aspirin therapy for stroke prevention in AF was restricted to those patients who refuse oral anticoagulation. Thirdly, the use of non-vitamin K antagonist oral anticoagulants [(NOACs), such as dabigatran, apixaban, and rivaroxaban)] was recommended in preference to vitamin K antagonists (VKAs) in most patients with a CHA2DS2-VASc score ≥1.[14]

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.[21]

In 2014, when the National Institute for Health and Care Excellence (NICE) updated its AF clinical guidelines (CG180),[22] 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.[23]

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).[24] 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 (i.e., 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 (e.g., smoking status, 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 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[14] and NICE 2014[22] guidance at index date (CHA2DS2-VASc score ≥2) were included in five cross-sectional analyses: on 1st April of 2012, 2013, 2014, and 2015 and 1st 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 (e.g., 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 vitamin K antagonists, apixaban, rivaroxaban, dabigatran, and parenteral AC. International normalised ratio (INR) measurements were treated as an indicator of VKA exposure and was therefore 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.[25]

Demographic characteristics included age, gender, and country of residence. Clinical characteristics were body mass index (BMI), 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 antiplatelet or nonsteroidal 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). CHA_2DS_2-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 READ 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% confidence interval were calculated 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 (FPFC = √(1-0.08) ~0.96).

An interrupted time series analysis [26] was conducted to estimate the impact of the updated ESC guidance (published in August 2012) and NICE 2014 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 (i.e., the rapid drop in rates immediately after the intervention) and trend (i.e., 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 anticoagulation management over time were also run separately in newly diagnosed patients with NVAF (<12 months) and in patients with NVAF with a diagnosis for ≥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 (GEE) were used to identify demographic and clinical characteristics associated withantiplatelet treatment , and with the absence of AT treatment (versus receiving anticoagulation therapy) 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 odds ratios and 95% confidence intervals.

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 version 9.4.

RESULTS

Patient Characteristics

The demographic and clinical characteristics of patients with NVAF eligible for anticoagulation according to ESC and NICE guidance (CHA2DS2-VASc ≥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 ≥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 ≥ 12 months). Similarly, the increase in the proportion of patients being prescribed AC was greater in those patients who were newly diagnosed compared to those diagnosed with NVAF for ≥ 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 ≥ 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, 21.5% rivaroxaban). No major change was observed in the NVAF population with a diagnosis for ≥ 12 months; VKA prescribed in 50.9% of the population in January 2016 and NOACs in 15% (including 4.5% apixaban, 2.2% dabigatran, 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 ≥ 12 months) showed that there was a significant trend for increasing anticoagulation treatment in both patient groups since April 2011 (Figure 3). However, a significant acceleration of this trend (increase of the slope) was observed after the updated ESC guidance publication (change in trend: β=+0.26 in newly diagnosed, β=+0.18 in patients diagnosed ≥ 12 months) and also after NICE guidance publication (change in trend: β=+0.12 in newly diagnosed, β=+0.15 in patients diagnosed ≥ 12 months).

Equally, a significant trend for decreasing antiplatelet 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: β=-0.26, post-NICE: β=-0.10) and after NICE for patients diagnosed ≥ 12 months (post-ESC: β=-0.15, post-NICE: β=-0.21).

Characteritics Associated with the Absence of Anticoagulation Therapy in April 2015

Tables 3 and 4 present the results of the GEE models comparing demographic and clinical characteristics in patients receiving either an AP alone or no AT, versus those receiving AC treatment in April 2015. Even after adjusting on CHA2DS2-VASc score, females, patients aged <65 and ≥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, CHA2DS2-VASc was associated with the absence of AT treatment, patients with a score ≥3 were less likely to remain untreated than patients with a CHA2DS2-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 to Wales and Northern Ireland.

DISCUSSION

A pronounced shift in anticoagulation management of patients with NVAF was observed in the UK between April 2012 and January 2016, coinciding with the update of ESC[14] and NICE[22] 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 1994-2003,[7, 8] no significant changes were observed in the years 2007–2010 in patients with CHA2DS2-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 (QOF) of the NHS (National Health

Service), which provided equal emphasis on AC and AP in stroke prevention in primary care at that time.[13]

The observed shift in treatment patterns in this study suggests a positive impact of both the ESC[14] and NICE[22] guidelines in driving changes in thrombopropylaxis strategy for NVAF patients 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 on GP's 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 longstanding 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 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 NOAC's (apixaban, rivaroxaban, 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[22] 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 ≥12 months, no major changes in the proportion treated with VKA were observed, indicating significant VKA inertia in this group.

Although these data show that anticoagulation treatment patterns in NVAF have improved substantially over the last five years, rates of anticoagulation appear to lag behind those observed in contemporary European cohorts. For example, at the two-year follow up of the EORP-AF registry in 2015, 79.2% of AF patients were identified as receiving at least one oral AC (compared to 62.9% in 2015 in this study, Table 2).[27] Rates of NOAC use however appear more comparable, with 13.7% of patients in EORP-AF receiving at least one NOAC (compared to 10.9% in this study in 2015). Baseline data from the European population of the 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.[28] These data are comparable to 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 GARFIELD-AF registry of patients with very recently diagnosed NVAF (<6 weeks), over the period from 2010/11 to 2014/15 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%), whilst AP monotherapy declined from 30.2% to 16.6%.[29] It is encouraging that our data up to January 2016 continue to show anticoagulation 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[22] relative to the ESC guidance in 2012.[14] 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 guideance in 2016.[30]

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 CHA2DS2-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 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[8, 12, 13, 31-35] and may be secondary to an overestimation of bleeding risk despite unequivocal evidence of the benefits of AC in the elderly.[36-39]

Our findings clearly illustrate the risk-treatment paradox previously reported in AF management [12] that patients at higher risk of stroke who more likely to benefit from AC therapy [38] 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.[40]

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.[8] Given that women with AF appear to lose their protection against sudden death including stroke,[41] and may even have a higher mortality than men,[42] 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 AF patients regardless of stroke risk, and may in fact cause harm [30] Altough the present study was conducted in the UK, the finding that a considerable number of AF patients 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 NVAF patients 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.[9, 43].

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.[44] 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 CRPD, 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, albeit 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 anticoagulation.

AUTHORSHIP DETAILS

L. Lacoin, C. Lefevre, D. Evans and J. Halcox conceived and designed the study. L. McDonald, M. Pereira and S. Ramagopalan undertook the analysis. All authors contributed to the analysis and interpretation of the data. L. McDonald wrote the first draft and all authors contributed to subsequent drafts and the final paper.

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FIGURE LEGENDS

Figure 1. Flowchart describing the sample used in each year

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 CHA2DS2-VASc ≥ 2 separately in newly diagnosed patients (A) and patients diagnosed since 12 months or more (B)

A) Newly diagnosed patients with NVAF

B) Patients with NVAF diagnosis since 12 months or more

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

A. Anticoagulation treatment

	Pre-ESC[1]			Post-ESC[2]			Post-NICE[2]		
	β	SE	p-value	β	SE	p-value	β	SE	p-value
Diagnosed < 12 months									
Level	43.09	0.26	<.0001	0.28	0.35	0.418	0.10	0.49	0.846
Trend	0.34	0.02	<.0001	0.26	0.03	<.0001	0.12	0.09	0.171
Diagnosed ≥ 12 months									
Level	49.01	0.07	<.0001	0.00	0.10	0.981	-0.16	0.14	0.251
Trend	0.13	0.01	<.0001	0.18	0.01	<.0001	0.15	0.02	<.0001

[1]For Pre-ESC data are base level, base trend. [2]Post-ESC and Post-NICE data are change in level, change in trend

B. Aspirin (ASA) or other AP only

	Pre-ESC[1]			Post-ESC[2]			Post-NICE[2]		
	β	SE	p-value	β	SE	p-value	β	SE	p-value
Diagnosed <12months									
Level	41.94	0.24	<.0001	-0.20	0.31	0.518	-0.63	0.44	0.159
Trend	-0.36	0.02	<.0001	-0.26	0.03	<.0001	-0.10	0.08	0.226
Diagnosed ≥12 months									
Level	35.05	0.06	<.0001	0.03	0.08	0.737	-0.33	0.12	0.008
Trend	-0.12	0.01	<.0001	-0.15	0.01	<.0001	-0.21	0.02	<.0001

[1]For Pre-ESC data are base level, base trend. [2]Post-ESC and Post-NICE data are change in level, change in trend

C. Without any antithrombotic treatment

	Pre-ESC[1]			Post-ESC[2]			Post-NICE[2]		
	β	SE	p-value	β	SE	p-value	β	SE	p-value
Diagnosed <12months									
Level	14.97	0.15	<.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 ≥12 months									
Level	15.94	0.07	<.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

[1]For Pre-ESC data are base level, base trend. [2]Post-ESC and Post-NICE data are change in level, change in trend

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

	April 2012 (n=67327)		April 2013 (n=66364)		April 2014 (n=62840)		April 2015 (n=53150)		Jan 2016 (n=45105)	
	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	51055	75.8	49721	74.9	45422	72.3	36910	69.4	28226	62.6
Wales	7193	10.7	7168	10.8	7658	12.2	6791	12.8	7088	15.7
Scotland	6826	10.1	7132	10.7	7331	11.7	6850	12.9	7060	15.7
Northern Ireland	2253	3.3	2343	3.5	2429	3.9	2599	4.9	2731	6.1
Smoking status										
Current smoker	4685	7.0	4500	6.8	4087	6.5	3305	6.2	2877	6.4
Past smoker	34297	50.9	34019	51.3	32258	51.3	27389	51.5	23119	51.3
Body mass index (kg/m^2)										
Missing data	5283	7.8	4588	6.9	3990	6.3	3209	6.0	2667	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	8197	12.2	8104	12.2	7421	11.8	6255	11.8	5564	12.3
Stroke risk factors										
Previous stroke/TIA	13136	19.5	12966	19.5	12312	19.6	10393	19.6	8986	19.9
Other arterial thromboembolism	281	0.4	267	0.4	243	0.4	207	0.4	182	0.4
Congestive heart failure	11970	17.8	11536	17.4	10780	17.2	9296	17.5	8272	18.3
Coronary artery disease	21158	31.4	20213	30.5	18691	29.7	15383	28.9	12892	28.6
Peripheral arterial disease	4136	6.1	3978	6	3671	5.8	2958	5.6	2491	5.5
Hypertension	65349	97.1	64557	97.3	61255	97.5	51872	97.6	44039	97.6
Diabetes mellitus	13949	20.7	13974	21.1	13564	21.6	11779	22.2	10222	22.7

	April 2012 (n=67327)		April 2013 (n=66364)		April 2014 (n=62840)		April 2015 (n=53150)		Jan 2016 (n=45105)	
	n	%	n	%	n	%	n	%	n	%
CHA2DS2-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 bleedings**	22136	32.9	22260	33.5	21770	34.6	18669	35.1	15889	35.2
Intracranial	1166	1.7	1223	1.8	1238	2.0	1039	2.0	897	2.0
Gastrointestinal	7755	11.5	7700	11.6	7575	12.1	6536	12.3	5677	12.6
Renal disease***	23367	34.7	23003	34.7	21391	34	17796	33.5	15061	33.4
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)	

Abbreviations: GP, general practitioner; NVAF, non-valvular atrial fibrillation; SD, standard deviation; TIA, transient ischaemic attack

* 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. Gynecological bleeds excluded.

*** Including any renal disease, chronic kidney disease stage 1-5

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 ≥ 2

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

Abbreviations: CI, confidence interval

Table 3. Factors associated with the prescription of aspirin or other antiplatelet for TE prevention in NVAF in April 2015 (vs. anticoagulation): results of the GEE model

	Antiplatelet therapy alone N=11,609		Treated with anticoagulant N= 33,413		OR (95% CI)	P-value
	n	%	N	%		
Patient age (years)						< .0001
< 65	890	7.7	2016	6.0	1.22 (1.10-1.35)	
65 to 74	2769	23.9	8780	26.3	Reference	
75 to 84	3842	33.1	14363	43.0	0.94 (0.87-1.02)	
≥ 85	4108	35.4	8254	24.7	1.72 (1.58-1.87)	
Country						0.001
England	8065	69.5	22909	68.6	Reference.	
Wales	1383	11.9	4524	13.5	0.80 (0.70-0.91)	
Scotland	1590	13.7	4231	12.7	1.06 (0.96-1.19)	
N. Ireland	571	4.9	1749	5.2	0.83 (0.72-0.97)	
Gender: male (reference = female)	5364	46.2	14580	43.6	0.87 (0.81-0.93)	<.0001
Time since NVAF diagnosis						<.0001
< 6 months	497	4.3	2121	6.3	Reference	
6 to 12 months	442	3.8	2175	6.5	0.96 (0.83-1.11)	
12 to 24 months	979	8.4	3886	11.6	1.24 (1.10-1.41)	
2 to 5 years since	3095	26.7	8496	25.4	1.89 (1.68-2.12)	
≥ 5 years	6596	56.8	16735	50.1	2.17 (1.93-2.44)	
Previous oral AC treatment						<.0001
No previous treatment	8093	69.7	21189	63.4	Reference	
NOAC only	87	0.7	411	1.2	0.61 (0.46-0.81)	
VKA and NOAC	76	0.7	490	1.5	0.37 (0.29-0.47)	
VKA only	3353	28.9	11323	33.9	0.65 (0.59-0.72)	
Previous stroke/TIA/arterial TE	2291	19.7	7341	22.0	0.83 (0.75-0.92)	0.0008
Congestive heart failure	1722	14.8	6685	20.0	0.61 (0.56-0.66)	<.0001
Previous coronary artery disease	4535	39.1	9636	28.8	1.60 (1.50--1.71)	<.0001

	Antiplatelet therapy alone N=11,609		Treated with anticoagulant N= 33,413		OR (95% CI)	P-value
	n	%	N	%		
Peripheral arterial disease	833	7.2	1887	5.6	1.20 (1.10-1.31)	0.0001
Hypertension	11308	97.4	32869	98.4	0.59 (0.51-0.69)	<.0001
CHA2DS2-VASc score						<.0001
2	1425	12.3	3444	10.3	Reference	
3	2408	20.7	7482	22.4	0.69 (0.63-0.76)	
4	3206	27.6	9656	28.9	0.56 (0.50-0.64)	
5	2306	19.9	6544	19.6	0.54 (0.46-0.64)	
≥6	2264	19.5	6287	18.9	0.52 (0.42-0.65)	
Previous bleed						<.0001
No bleed	7522	64.8	21577	64.6	Reference	
Intracranial bleed	346	3.0	404	1.2	3.02 (2.56-3.56)	
Gastrointestinal bleed	1430	12.3	4001	11.8	0.96 (0.90-1.02)	
Other bleed	2311	19.9	7473	22.4	0.82 (0.77-0.87)	
History of fall	3474	29.9	8211	24.6	1.14 (1.08-1.20)	<.0001
Renal disease	4106	35.4	11542	34.5	0.94 (0.90-0.99)	0.0131
Liver disease	102	0.9	214	0.6	1.32 (1.03-1.70)	0.0414
Number of comedications						<.0001
< 5	1448	12.5	6879	20.6	Reference	
5 to 9	5040	43.4	14825	44.4	1.71 (1.60-1.82)	
10 to 14	3169	27.3	7782	23.3	2.08 (1.93-2.26)	
15 or more	1952	16.8	3927	11.8	2.66 (2.43-2.91)	

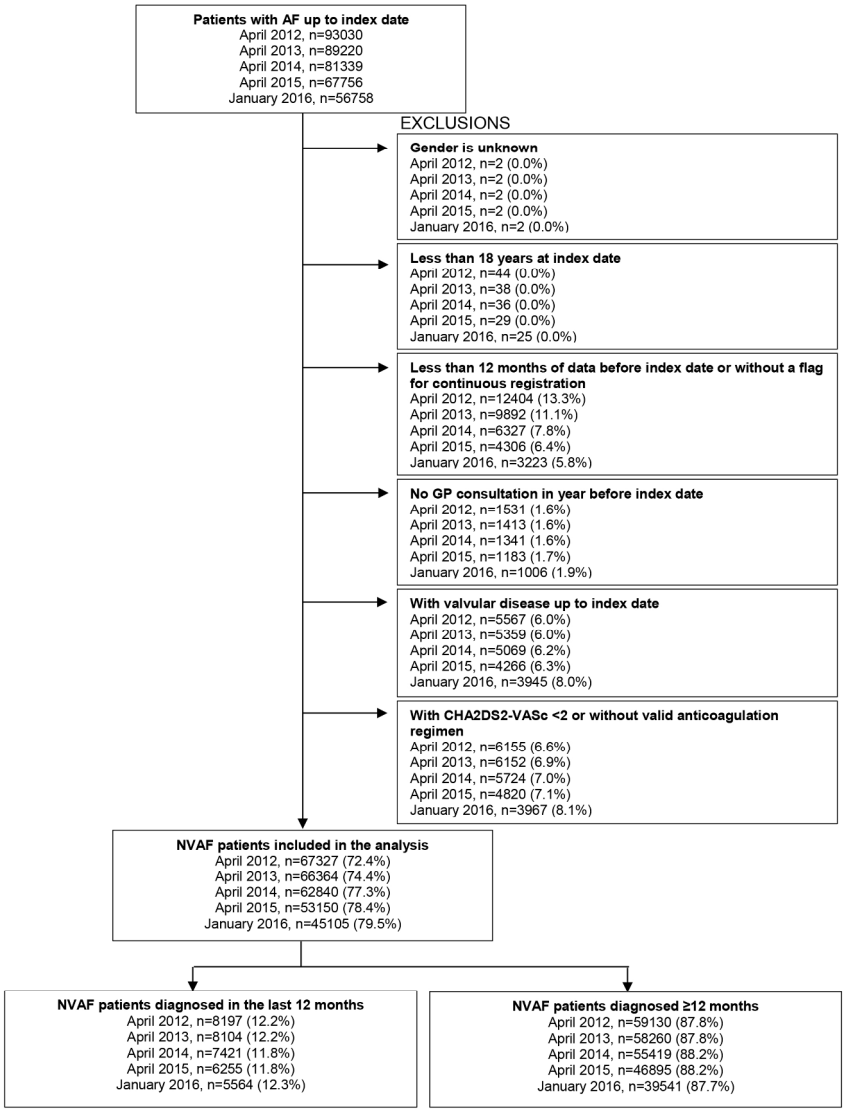
Abbreviations: CI, confidence interval; GEE, generalised estimating equations; VKA, vitamin K antagonist; OAC, oral anticoagulant; NVAF, non-valvular atrial fibrillation; TIA, transient ischaemic attack; TE, thromboembolism; OR, odds ratio; NOAC, novel oral anticoagulant.

Table 4. 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=8,128		Treated with anticoagulant N= 33,413		OR (95% CI)	P-value
	n	%	n	%		
Patient age (years)						<.0001
< 65	1299	16	2016	6.0	1.64 (1.47-1.83)	
65 to 74	2214	27.2	8780	26.3	Reference	
75 to 84	2367	29.1	14363	43.0	1.09 (0.99-1.20)	
≥ 85	2248	27.7	8254	24.7	1.86 (1.68-2.07)	
Gender: male (reference = female)	4450	54.7	14580	43.6	0.51 (0.46-0.56)	<.0001
Country						
England	5936	73.0	22909	68.6	Reference	<.0001
Wales	884	10.9	4524	13.5	0.80 (0.69-0.93)	
Scotland	1029	12.7	4231	12.7	1.09 (0.96-1.23)	
Northern Ireland	279	3.4	1749	5.2	0.69 (0.57-0.83)	
Time since NVAF diagnosis						<.0001
< 6 months	592	7.3	2121	6.3	Reference	
6 to 12 months	427	5.3	2175	6.5	0.71 (0.61-0.82)	
12 to 24 months	864	10.6	3886	11.6	0.82 (0.71-0.94)	
2 to 5 years	2086	25.7	8496	25.4	0.93 (0.82-1.06)	
≥ 5 years	4159	51.2	16735	50.1	1.07 (0.94-1.23)	
Previous OAC treatment						<.0001
No previous OAC	5137	63.2	21189	63.4	Reference	
NOAC only	189	2.3	411	1.2	1.82 (1.36-2.43)	
VKA and NOAC	159	2.0	490	1.5	1.50 (1.23-1.84)	
VKA only	2643	32.5	11323	33.9	0.97 (0.88-1.07)	
Previous stroke/TIA/ arterial TE	968	11.9	7341	22.0	0.55 (0.48-0.64)	<.0001
Congestive heart failure	889	10.9	6685	20.0	0.76 (0.69-0.84)	<.0001

Parameter	No antithrombotic therapy N=8,128		Treated with anticoagulant N= 33,413		OR (95% CI)	P-value
	n	%	n	%		
Previous coronary artery disease	1212	14.9	9636	28.8	0.76 (0.70-0.84)	<.0001
Hypertension	7695	94.7	32869	98.4	0.62 (0.53-0.72)	<.0001
CHA2DS2-VASc score						<.0001
2	2212	27.2	3444	10.3	Reference	
3	2034	25	7482	22.4	0.48 (0.43-0.54)	
4	2057	25.3	9656	28.9	0.33 (0.28-0.39)	
5	987	12.1	6544	19.6	0.28 (0.22-0.35)	
≥6	838	10.27	6287	18.9	0.27 (0.20-0.36)	
Previous bleed						<.0001
No bleed	5382	66.2	21577	64.6	Reference	
IC bleed	289	3.6	404	1.2	8.03 (6.43-10.02)	
GI bleed	1016	12.5	4001	11.8	1.24 (1.14-1.35)	
Other bleed	1441	17.7	7473	22.4	0.91 (0.85-0.97)	
History of peptic ulcer	465	5.7	1743	5.2	1.36 (1.21-1.52)	<.0001
History of anaemia	227	2.8	880	2.6	1.44 (1.24-1.67)	<.0001
History of fall	2097	25.8	8211	24.6	1.20 (1.13-1.28)	<.0001
Renal disease	2148	26.4	11542	34.5	0.90 (0.84-0.96)	0.0016
Liver disease	109	1.3	214	0.6	2.39 (1.87-3.05)	<.0001
Active cancer	455	3.9	1367	4.1	1.19 (1.06-1.35)	0.0053
Number of co-medications						<.0001
< 5	3384	41.6	6879	20.6	Reference	
5 to 9	2791	34.3	14825	44.4	0.49 (0.45-0.52)	
10 to 14	1271	15.6	7782	23.3	0.46 (0.43-0.50)	
≥15	682	8.4	3927	11.8	0.53 (0.48-0.59)	

Abbreviations: CI, confidence interval; GEE, generalised estimating equations; VKA, vitamin K antagonist; OAC, oral anticoagulant; NVAF, non-valvular atrial fibrillation; TIA, transient ischaemic attack; TE, thromboembolism; OR, odds ratio; NOAC, novel oral anticoagulant



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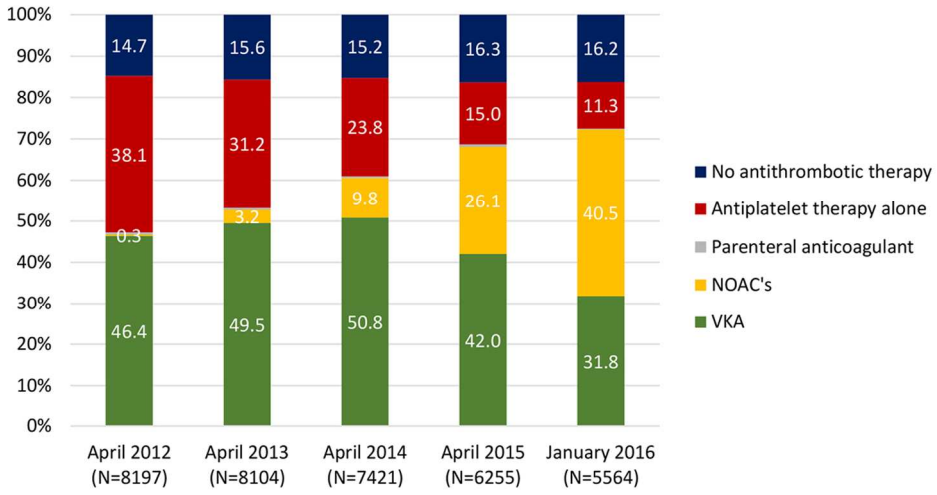

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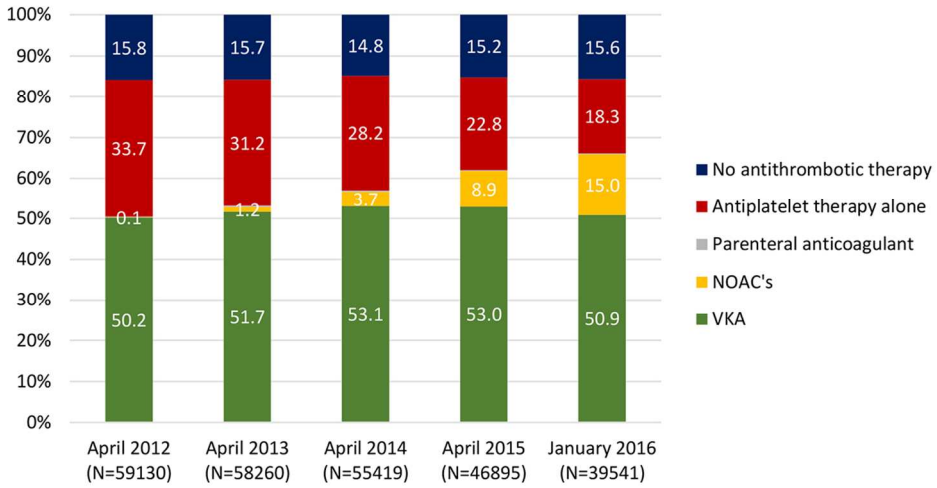

FIgure 2

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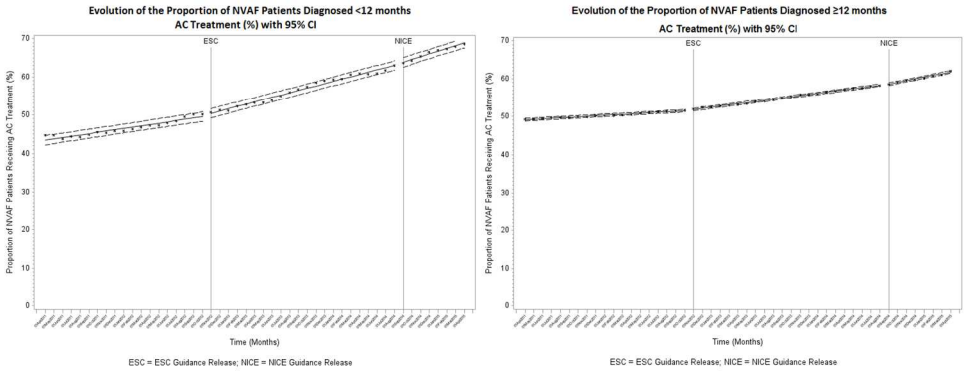

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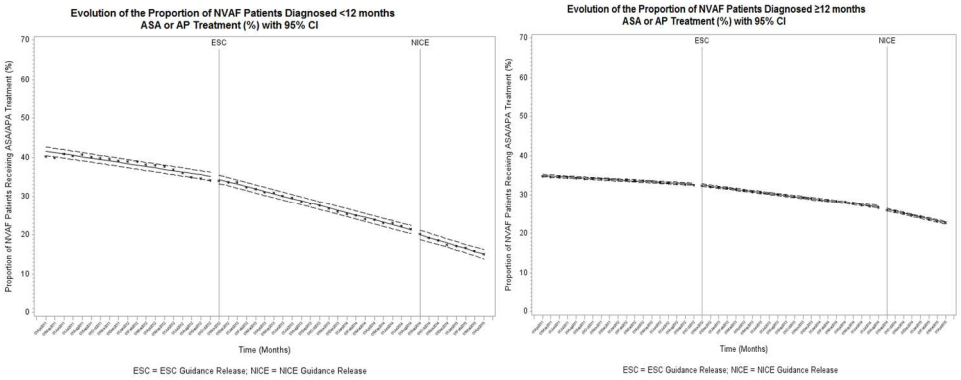

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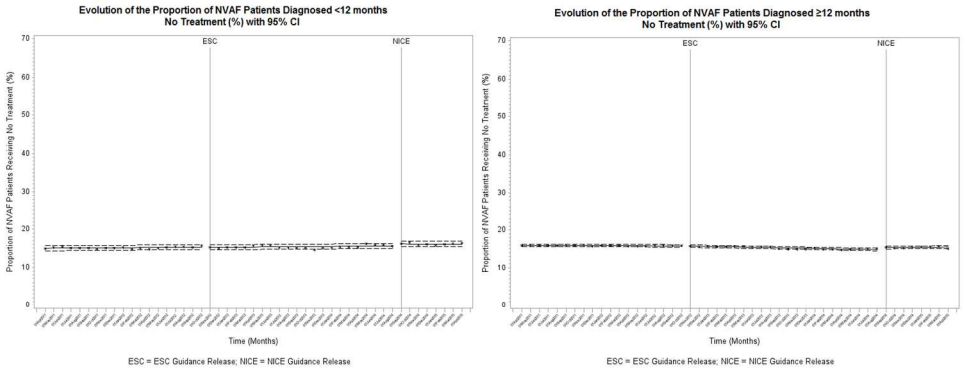

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DATA SUPPLEMENT

Table s1. READ code descriptions

G11..00	Mitral valve diseases
G540.15	Mitral valve prolapse
G110.00	Mitral stenosis
G540.00	Mitral valve incompetence
G541.00	Aortic valve disorders
G540000	Mitral incompetence, non-rheumatic
G130.00	Mitral and aortic stenosis
G13..00	Diseases of mitral and aortic valves
G541400	Aortic valve stenosis with insufficiency
G131.14	Mitral stenosis and aortic regurgitation
G544200	Combined disorders of mitral, aortic and tricuspid valves
G541z00	Aortic valve disorders NOS
G544100	Disorders of both mitral and tricuspid valves
G540z00	Mitral valve disorders NOS
G113.00	Nonrheumatic mitral valve stenosis
G13z.00	Mitral and aortic valve disease NOS
G11z.00	Mitral valve disease NOS
G133.00	Mitral and aortic incompetence
G132.12	Mitral incompetence and aortic stenosis
G540200	Mitral valve prolapse
G132.00	Mitral insufficiency and aortic stenosis
G132.13	Mitral regurgitation and aortic stenosis
G540100	Mitral incompetence, cause unspecified
G540300	Mitral valve leaf prolapse
G544.00	Multiple valve diseases
G540.12	Mitral valve insufficiency
G112.13	Mitral stenosis with regurgitation
G112.00	Mitral stenosis with insufficiency
Gyu5600	[X]Other aortic valve disorders
G131.00	Mitral stenosis and aortic insufficiency
G12z.00	Rheumatic aortic valve disease NOS
G112.12	Mitral stenosis with incompetence
Gyu1000	[X]Other mitral valve diseases
P65..00	Congenital mitral stenosis

G544X00	Multiple valve disease, unspecified
G114.00	Ruptured mitral valve cusp
G131.13	Mitral stenosis and aortic incompetence
P66..00	Congenital mitral insufficiency
P652.00	Parachute deformity of the mitral valve
G13y.00	Multiple mitral and aortic valve involvement
Gyu5A00	[X]Aortic valve disorders in diseases classified elsewhere
P650.00	Congenital mitral stenosis, unspecified
G133.11	Mitral and aortic insufficiency
Gyu5500	[X]Other nonrheumatic mitral valve disorders
P65z.00	Congenital mitral stenosis NOS
Gyu5D00	[X]Multiple valve disorders/diseases CE
READ Codes for prosthetic valve description	
7911.12	Replacement of aortic valve
P641.00	Bicuspid aortic valve
7910300	Replacement of mitral valve NEC
7910.12	Replacement of mitral valve
7910.12	Replacement of mitral valve
7914300	Replacement of valve of heart NEC
7914200	Prosthetic replacement of valve of heart NEC
7910.00	Plastic repair of mitral valve
7911.00	Plastic repair of aortic valve
7911300	Replacement of aortic valve NEC
7915000	Revision of plastic repair of mitral valve
7916000	Open mitral valvotomy
7917000	Closed mitral valvotomy
7910200	Prosthetic replacement of mitral valve
7910200	Prosthetic replacement of mitral valve
7910400	Mitral valvuloplasty NEC
ZV43300	[V]Has artificial heart valve
7914.11	Replacement of unspecified valve of heart
7910211	Bjork-Shiley prosthetic replacement of mitral valve
7911200	Prosthetic replacement of aortic valve
7910.11	Mitral valvuloplasty
7914212	Starr prosthetic replacement of valve of heart
7911100	Xenograft replacement of aortic valve

7911y00	Other specified plastic repair of aortic valve
ZV45H00	[V]Presence of prosthetic heart valve
7910z00	Plastic repair of mitral valve NOS
7911000	Allograft replacement of aortic valve
7915100	Revision of plastic repair of aortic valve
7914211	Edwards prosthetic replacement of valve of heart
TB01200	Implant of heart valve prosthesis + complication, no blame
7910213	Carpentier prosthetic replacement of mitral valve
7910100	Xenograft replacement of mitral valve
7919000	Percutaneous transluminal mitral valvotomy
7911z00	Plastic repair of aortic valve NOS
7910212	Bjork-Shiley prosthetic replacement of mitral valve
7910y00	Other specified plastic repair of mitral valve
SP00200	Mechanical complication of heart valve prosthesis
SyuK611	[X] Embolism from prosthetic heart valve
790D700	Replacement of valved cardiac conduit
7914100	Xenograft replacement of valve of heart NEC
7914000	Allograft replacement of valve of heart NEC
ZVu6e00	[X]Presence of other heart valve replacement
7910214	Edwards prosthetic replacement of mitral valve
7910411	Mitral valve repair NEC
7911411	Aortic valve repair NEC
7910000	Allograft replacement of mitral valve
7911600	Transluminal aortic valve implantation
7911500	Transapical aortic valve implantation
7914600	Replacement of truncal valve
7918000	Annuloplasty of mitral valve

Table s2. Proportion of patients with NVAF treated in April 2012, 2013, 2014, and 2015 in the UK, according to duration of diagnosis

	April 2012 % [95% CI]	April 2013 % [95% CI]	April 2014 % [95% CI]	April 2015 % [95% CI]	January 2016 % [95% CI]
Diagnosed < 12 months					
Anticoagulation treatment	**47.2 [46.2-48.3]**	**53.2 [52.1-54.2]**	**61.0 [59.9-62.0]**	**68.7 [67.6-69.8]**	**72.5 [71.3-73.7]**
VKA	46.4 [45.4-47.4]	49.5 [48.5-50.6]	50.8 [49.7-51.9]	42.0 [40.8-43.1]	31.8 [30.6-33.0]
Apixaban	-	-	1.7 [1.5-2.0]	8.8 [8.1-9.5]	16.6 [15.6-17.5]
Rivaroxaban	-	1.2 [1.0-1.5]	5.5 [5.0-6.0]	14.5 [13.7-15.3]	21.5 [20.4-22.6]
Dabigatran	0.3 [0.2-0.4]	2.0 [1.7-2.3]	2.6 [2.3-2.9]	2.8 [2.5-3.2]	2.4 [2.0-2.8]
Parenteral anticoagulant	0.5 [0.4-0.6]	0.5 [0.3-0.6]	0.4 [0.2-0.5]	0.6 [0.4-0.8]	0.2 [0.1-0.4]
Antiplatelet therapy alone	**38.1 [37-39.1]**	**31.2 [30.2-32.1]**	**23.8 [22.9-24.8]**	**15 [14.2-15.9]**	**11.3 [10.5-12.1]**
No antithrombotic therapy	**14.7 [14-15.4]**	**15.6 [14.9-16.4]**	**15.2 [14.4-16]**	**16.3 [15.4-17.2]**	**16.2 [15.2-17.1]**
Diagnosed ≥ 12 months					
Anticoagulation treatment	**50.6 [50.2-51.0]**	**53.2 [52.8-53.5]**	**57.0 [56.6-57.4]**	**62.1 [61.7-62.5]**	**66.1 [65.6-66.6]**
VKA	50.2 [49.8-50.6]	51.7 [51.3-52.1]	53.1 [52.7-53.5]	53.0 [52.5-53.4]	50.9 [50.4-51.4]
Apixaban	-	-	0.4 [0.3-0.4]	2.0 [1.9-2.1]	4.5 [4.3-4.7]
Rivaroxaban	-	0.5 [0.4-0.5]	1.9 [1.8-2.0]	4.9 [4.7-5.1]	8.3 [8.0-8.6]
Dabigatran	0.1 [0.1-0.1]	0.7 [0.7-0.8]	1.4 [1.3-1.5]	2.0 [1.9-2.1]	2.2 [2.1-2.4]
Parenteral anticoagulant	0.2 [0.2-0.3]	0.3 [0.2-0.3]	0.3 [0.2-0.3]	0.2 [0.2-0.3]	0.2 [0.2-0.3]
Antiplatelet therapy alone	**33.7 [33.3-34.0]**	**31.2 [30.8-31.5]**	**28.2 [27.8-28.5]**	**22.8 [22.4-23.1]**	**18.3 [17.9-18.7]**
No antithrombotic therapy	**15.8 [15.5-16.0]**	**15.7 [15.4-16.0]**	**14.8 [14.5-15.1]**	**15.2 [14.8-15.5]**	**15.6 [15.3-16.0]**

Abbreviations: CI, confidence interval; VKA, vitamin K antagonists

Table s3. Proportion of patients with NVAF treated in April 2012, 2013, 2014, and 2015 in the UK,. according to country of residence

	April 2012 % [95% CI]	April 2013 % [95% CI]	April 2014 % [95% CI]	April 2015 % [95% CI]	January 2016 % [95% CI]
England					
Anticoagulation treatment	**49.6 [49.2-50]**	**52.4 [52-52.9]**	**56.9 [56.5-57.4]**	**62.1 [61.6-62.5]**	**66.5 [66.0-67.1]**
VKA	49.2 [48.8-49.6]	50.8 [50.4-51.2]	52.4 [51.9-52.8]	51.3 [50.8-51.8]	47.9 [47.4-48.5]
Apixaban	-	-	0.4 [0.4-0.5]	2.3 [2.2-2.5]	5.0 [4.8-5.3]
Rivaroxaban	-	0.5 [0.4-0.5]	2.1 [2.0-2.2]	5.7 [5.5-5.9]	10.7 [10.3-11.0]
Dabigatran	0.1 [0.1-0.1]	0.9 [0.8-1.0]	1.7 [1.6-1.8]	2.4 [2.3-2.6]	2.6 [2.4-2.8]
Parenteral anticoagulant	0.3 [0.2-0.3]	0.3 [0.2-0.3]	0.3 [0.3-0.4]	0.3 [0.3-0.4]	0.2 [0.2-0.3]
Antiplatelet therapy alone	**33.9 [33.5-34.3]**	**30.9 [30.6-31.3]**	**27.5 [27.1-27.9]**	**21.9 [21.4-22.3]**	**17.0 [16.5-17.4]**
No antithrombotic therapy	**16.5 [16.2-16.8]**	**16.6 [16.3-16.9]**	**15.6 [15.3-15.9]**	**16.1 [15.7-16.4]**	**16.5 [16.1-17.0]**
Scotland					
Anticoagulation treatment	**48.8 [47.7-49.9]**	**51.9 [50.8-53]**	**55.5 [54.4-56.6]**	**61.8 [60.7-62.9]**	**64.3 [63.2-65.4]**
VKA	48.2 [47.1-49.3]	49.2 [48.1-50.3]	49.1 [48.0-50.2]	48.4 [47.2-49.5]	45.2 [44-46.3]
Apixaban	-	-	0.5 [0.3-0.6]	2.7 [2.3-3.0]	6.6 [6.0-7.2]
Rivaroxaban	-	1.8 [1.5-2.0]	5.0 [4.5-5.4]	9.8 [9.1-10.5]	11.6 [10.8-12.3]
Dabigatran	0.4 [0.2-0.5]	0.5 [0.4-0.7]	0.7 [0.5-0.8]	0.7 [0.5-0.8]	0.8 [0.6-1.0]
Parenteral anticoagulant	0.2 [0.1-0.3]	0.4 [0.2-0.5]	0.3 [0.2-0.4]	0.2 [0.1-0.3]	0.1 [0.1-0.2]
Antiplatelet therapy alone	**37 [35.9-38.1]**	**33.6 [32.6-34.7]**	**29.6 [28.6-30.6]**	**23.2 [22.3-24.2]**	**19.9 [19.0-20.8]**
No antithrombotic therapy	**14.2 [13.4-15.0]**	**14.5 [13.7-15.3]**	**14.9 [14.2-15.7]**	**15 [14.2-15.8]**	**15.8 [14.9-16.6]**
Wales					
Anticoagulation treatment	**55.1 [54.0-56.2]**	**58.7 [57.7-59.8]**	**61.7 [60.6-62.7]**	**66.6 [65.5-67.7]**	**69.1 [68.0-70.2]**
VKA	54.8 [53.7-55.9]	57.6 [56.5-58.7]	59.1 [58.0-60.1]	59.3 [58.1-60.4]	57.6 [56.5-58.8]
Apixaban	-	0.0 [0.0-0.1]	0.3 [0.2-0.4]	2.2 [1.9-2.5)	3.9 [3.4-4.3]
Rivaroxaban	-	0.1 [0.0-0.2]	0.9 [0.7-1.1]	3.2 [2.8-3.6)	5.1 [4.6-5.6]
Dabigatran	0.0 [0.0-0.1]	0.9 [0.6-1.1]	1.3 [1.1-1.5]	1.9 [1.6-2.2]	2.3 [2.0-2.7]
Parenteral anticoagulant	0.2 [0.1-0.3]	0.2 [0.1-0.3]	0.1 [0.1-0.2]	0.1 [0.0-0.1]	0.2 [0.1-0.2]
Antiplatelet therapy alone	**32.5 [31.5-33.6]**	**29.4 [28.4-30.4]**	**26.7 [25.8-27.7]**	**20.4 [19.4-21.3]**	**16.8 [15.9-17.7]**
No antithrombotic therapy	**12.4 [11.6-13.1]**	**11.9 [11.2-12.6]**	**11.6 [10.9-12.3]**	**13.0 [12.2-13.8]**	**14.1 [13.3-14.9]**
Northern Ireland					
Anticoagulation treatment	**51.5 [49.6-53.5]**	**55 [53.0-56.9]**	**60.8 [59.0-62.7]**	**67.3 [65.6-69.0]**	**71.9 [70.2-73.6]**
VKA	50.7 [48.7-52.7]	52.4 [50.4-54.3]	51.5 [49.6-53.4]	46 [44.2-47.9]	39.7 [37.9-41.6]
Apixaban	-	0.1 [0.0-0.2]	3.1 [2.4-3.7]	11.1 [10.0-12.3]	19.1 [17.6-20.6]
Rivaroxaban	-	0.4 [0.1-0.6]	3.5 [2.8-4.2]	7.5 [6.5-8.4]	10.7 [9.5-11.8]
Dabigatran	0.5 [0.2-0.8)	1.6 [1.1-2.1]	2.5 [1.9-3.1]	2.3 [1.8-2.9]	2.1 [1.6-2.7]

Management of NVAF in Europe and the UK

	April 2012 % [95% CI]	April 2013 % [95% CI]	April 2014 % [95% CI]	April 2015 % [95% CI]	January 2016 % [95% CI]
Parenteral anticoagulant	0.3 [0.1-0.5]	0.6 [0.3-0.8]	0.2 [0.1-0.4]	0.3 [0.1-0.6]	0.3 [0.1-0.5]
Antiplatelet therapy alone	**37.9 [35.9-39.8]**	**34.1 [32.2-35.9]**	**28.2 [26.4-29.9]**	**22 [20.4-23.5]**	**17.2 [15.8-18.6]**
No antithrombotic therapy	**10.6 [9.4-11.8]**	**11 [9.8-12.2]**	**11.0 [9.8-12.2]**	**10.7 [9.6-11.9]**	**10.9 [9.8-12.1]**

Abbreviations: CI, confidence interval; VKA, vitamin K antagonists

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any pre-specified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4-5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4-5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	n/a
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4-5
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	n/a
		(*c*) Explain how missing data were addressed	n/a
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	10
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	20
		(b) Give reasons for non-participation at each stage	20
		(c) Consider use of a flow diagram	20
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	16
		(b) Indicate number of participants with missing data for each variable of interest	16
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	n/a
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	n/a
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	n/a
		Cross-sectional study—Report numbers of outcome events or summary measures	6, 16, 17-19
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	17
		(*b*) Report category boundaries when continuous variables were categorized	18-19
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10
Discussion			
Key results	18	Summarise key results with reference to study objectives	8
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9-10
Generalisability	21	Discuss the generalisability (external validity) of the study results	10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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The evolving landscape of stroke prevention in atrial fibrillation within the United Kingdom between 2012 and 2016 - a cross sectional analysis study using CPRD

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The evolving landscape of stroke prevention in atrial fibrillation within the United Kingdom 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 non-valvular atrial fibrillation (NVAF) and eligible for anticoagulation (CHA2DS2-VASc score ≥ 2) on 1st 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.

STRENGTHS AND LIMITATIONS

- A large representative population of patients with all forms of AF (paroxysmal, chronic) studied in the 'real-world' using data obtainted from GP 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 auditied 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 AC prescriptions is secondary care

Key words: Atrial Fibrillation, Drug Therapy, Electronic Health Records, Great Britain, Stroke

INTRODUCTION

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

Approximately 20% of stroke cases in the United Kingdom (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.[5, 6] However, AF-related strokes can be prevented and their impact minimised by effective management strategies including increased detection of AF, adherence to stroke prevention guidelines and anticoagulant (AC) use in at-risk patients.

Although anticoagulation is effective in preventing strokes due to AF, evidence suggests anticoagulation therapy remains underused.[7-13] In 2010, Holt et al. 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.[9] 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.[14] This update included three major changes based on new or strengthened evidence. Firstly, the CHA2DS2-VASc score replaced the CHADS2 score for the assessment of stroke risk. This is based on the accumulated evidence that CHA2DS2-VASc score, which is inclusive of the most common risk factors for stroke[15] and has been validated in multiple cohorts,[16] is better at identifying patients at “truly low risk” of AF-related stroke.[17-20] Secondly, the use of aspirin therapy for stroke prevention in AF was restricted to those patients who refuse oral anticoagulation. Thirdly, the use of non-vitamin K antagonist oral anticoagulants [(NOACs), such as dabigatran, apixaban, and rivaroxaban)] was recommended in preference to vitamin K antagonists (VKAs) in most patients with a CHA2DS2-VASc score ≥1.[14]

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.[21]

In 2014, when the National Institute for Health and Care Excellence (NICE) updated its AF clinical guidelines (CG180),[22] 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.[23]

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).[24] 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 (i.e., 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 (e.g., smoking status, 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 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[14] and NICE 2014[22] guidance at index date (CHA2DS2-VASc score ≥2) were included in five cross-sectional analyses: on 1st April of 2012, 2013, 2014, and 2015 and 1st 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 (e.g., 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 vitamin K antagonists, apixaban, rivaroxaban, dabigatran, and parenteral AC. International normalised ratio (INR) measurements were treated as an indicator of VKA exposure and was therefore 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.[25]

Demographic characteristics included age, gender, and country of residence. Clinical characteristics were body mass index (BMI), 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 antiplatelet or nonsteroidal 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). CHA_2DS_2-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 READ 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% confidence interval were calculated 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 (FPFC = √(1-0.08) ~0.96).

An interrupted time series analysis [26] was conducted to estimate the impact of the updated ESC guidance (published in August 2012) and NICE 2014 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 (i.e., the rapid drop in rates immediately after the intervention) and trend (i.e., 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 anticoagulation management over time were also run separately in newly diagnosed patients with NVAF (<12 months) and in patients with NVAF with a diagnosis for ≥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 (GEE) were used to identify demographic and clinical characteristics associated withantiplatelet treatment , and with the absence of AT treatment (versus receiving anticoagulation therapy) 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 odds ratios and 95% confidence intervals.

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 version 9.4.

RESULTS

Patient Characteristics

The demographic and clinical characteristics of patients with NVAF eligible for anticoagulation according to ESC and NICE guidance (CHA2DS2-VASc ≥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 ≥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 ≥ 12 months). Similarly, the increase in the proportion of patients being prescribed AC was greater in those patients who were newly diagnosed compared to those diagnosed with NVAF for ≥ 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 ≥ 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, 21.5% rivaroxaban). No major change was observed in the NVAF population with a diagnosis for ≥ 12 months; VKA prescribed in 50.9% of the population in January 2016 and NOACs in 15% (including 4.5% apixaban, 2.2% dabigatran, 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 ≥ 12 months) showed that there was a significant trend for increasing anticoagulation treatment in both patient groups since April 2011 (Figure 3). However, a significant acceleration of this trend (increase of the slope) was observed after the updated ESC guidance publication (change in trend: β=+0.26 in newly diagnosed, β=+0.18 in patients diagnosed ≥ 12 months) and also after NICE guidance publication (change in trend: β=+0.12 in newly diagnosed, β=+0.15 in patients diagnosed ≥ 12 months).

Equally, a significant trend for decreasing antiplatelet 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: β=-0.26, post-NICE: β=-0.10) and after NICE for patients diagnosed ≥ 12 months (post-ESC: β=-0.15, post-NICE: β=-0.21).

Characteritics Associated with the Absence of Anticoagulation Therapy in April 2015

Tables 3 and 4 present the results of the GEE models comparing demographic and clinical characteristics in patients receiving either an AP alone or no AT, versus those receiving AC treatment in April 2015. Even after adjusting on CHA2DS2-VASc score, females, patients aged <65 and ≥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, CHA2DS2-VASc was associated with the absence of AT treatment, patients with a score ≥3 were less likely to remain untreated than patients with a CHA2DS2-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 to Wales and Northern Ireland.

DISCUSSION

A pronounced shift in anticoagulation management of patients with NVAF was observed in the UK between April 2012 and January 2016, coinciding with the update of ESC[14] and NICE[22] 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 1994-2003,[7, 8] no significant changes were observed in the years 2007–2010 in patients with CHA2DS2-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 (QOF) of the NHS (National Health

Service), which provided equal emphasis on AC and AP in stroke prevention in primary care at that time.[13]

The observed shift in treatment patterns in this study suggests a positive impact of both the ESC [14] and NICE[22] guidelines in driving changes in thrombopropylaxis strategy for NVAF patients 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 on GP's 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 longstanding 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 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 NOAC's (apixaban, rivaroxaban, 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[22] 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 ≥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 NOAC's in newly diagnosied AF patients can be linked to a growing awareness raised through NICE guidance about the benefits of NOAC treatment but also to an increased attentiveness to AF detection. Currently, only opportunistic screening for AF is implemeneted: - NICE recommends an ECG to diagnose AF in patients who present with irregular pulse[22], 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 anticoagulation treatment patterns in NVAF have improved substantially over the last five years, rates of anticoagulation appear to lag behind those observed in contemporary European cohorts. For example, at the two-year follow up of the EORP-AF registry in 2015, 79.2% of AF patients were identified as receiving at least one oral AC (compared to 62.9% in 2015 in this study, Table 2).[27] Rates of NOAC use however appear more comparable, with 13.7% of patients in EORP-AF receiving at least one NOAC (compared to 10.9% in this study in 2015). Baseline data from the European population of the 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.[28] These data are comparable to 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 GARFIELD-AF registry of patients with very recently diagnosed NVAF (<6 weeks), over the period from 2010/11 to 2014/15 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%), whilst AP monotherapy declined from 30.2% to 16.6%.[29] It is

encouraging that our data up to January 2016 continue to show anticoagulation 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[22] relative to the ESC guidance in 2012.[14] 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 guideance in 2016.[30]

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 CHA2DS2-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 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[8, 12, 13, 31-35] and may be secondary to an overestimation of bleeding risk despite unequivocal evidence of the benefits of AC in the elderly.[36-39]

Our findings clearly illustrate the risk-treatment paradox previously reported in AF management [12] that patients at higher risk of stroke who more likely to benefit from AC therapy [38] 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.[40]

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.[8] Given that women with AF appear to lose their protection against sudden death including stroke,[41] and may even have a higher mortality than men,[42] 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 AF patients regardless of stroke risk, and may in fact cause harm [30] Altough the present study was conducted in the UK, the finding that a considerable number of AF patients 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 NVAF patients 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.[9, 43].

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.[44] 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 CRPD, 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, albeit 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 anticoagulation.

AUTHORSHIP DETAILS

L. Lacoin, C. Lefevre, D. Evans and J. Halcox conceived and designed the study. L. McDonald, M. Pereira and S. Ramagopalan undertook the analysis. All authors (LL, ML, ER, MP, LM, SR, CL, DE and JH) contributed to the analysis and interpretation of the data. L. McDonald and L Lacoin wrote the first draft and all authors contributed to subsequent drafts and the final paper.

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COMPETING INTERESTS

All authors have completed the ICMJE uniform disclosure form. MP, LM and SR were employees of Evidera who were paid consultants to Bristol-Myers Squibb (BMS) in connection with conducting this study and with the development of this manuscript. JH received consultancy fees from BMS for the conduct of this study. DE, ER, CL and LL were BMS employees at the time of the research. ML is a fulltime employee of Pfizer.

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DATA SHARING STATEMENT

No additional data is available for sharing.

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FIGURE LEGENDS

Figure 1. Flowchart describing the sample used in each year

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 CHA2DS2-VASc ≥ 2 separately in newly diagnosed patients (A) and patients diagnosed since 12 months or more (B)

A) Newly diagnosed patients with NVAF

B) Patients with NVAF diagnosis since 12 months or more

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

A. Anticoagulation treatment

	Pre-ESC[1]			**Post-ESC[2]**			**Post-NICE[2]**		
	β	SE	p-value	β	SE	p-value	β	SE	p-value
Diagnosed < 12 months									
Level	43.09	0.26	<.0001	0.28	0.35	0.418	0.10	0.49	0.846
Trend	0.34	0.02	<.0001	0.26	0.03	<.0001	0.12	0.09	0.171
Diagnosed ≥ 12 months									
Level	49.01	0.07	<.0001	0.00	0.10	0.981	-0.16	0.14	0.251
Trend	0.13	0.01	<.0001	0.18	0.01	<.0001	0.15	0.02	<.0001

[1]For Pre-ESC data are base level, base trend. [2]Post-ESC and Post-NICE data are change in level, change in trend

B. Aspirin (ASA) or other AP only

	Pre-ESC[1]			Post-ESC[2]			Post-NICE[2]		
	β	SE	p-value	β	SE	p-value	β	SE	p-value
Diagnosed <12months									
Level	41.94	0.24	<.0001	-0.20	0.31	0.518	-0.63	0.44	0.159
Trend	-0.36	0.02	<.0001	-0.26	0.03	<.0001	-0.10	0.08	0.226
Diagnosed ≥12 months									
Level	35.05	0.06	<.0001	0.03	0.08	0.737	-0.33	0.12	0.008
Trend	-0.12	0.01	<.0001	-0.15	0.01	<.0001	-0.21	0.02	<.0001

[1]For Pre-ESC data are base level, base trend. [2]Post-ESC and Post-NICE data are change in level, change in trend

C. Without any antithrombotic treatment

	Pre-ESC[1]			Post-ESC[2]			Post-NICE[2]		
	β	SE	p-value	β	SE	p-value	β	SE	p-value
Diagnosed <12months									
Level	14.97	0.15	<.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 ≥12 months									
Level	15.94	0.07	<.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

[1]For Pre-ESC data are base level, base trend. [2]Post-ESC and Post-NICE data are change in level, change in trend

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

	April 2012 (n=67327)		April 2013 (n=66364)		April 2014 (n=62840)		April 2015 (n=53150)		Jan 2016 (n=45105)	
	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	51055	75.8	49721	74.9	45422	72.3	36910	69.4	28226	62.6
Wales	7193	10.7	7168	10.8	7658	12.2	6791	12.8	7088	15.7
Scotland	6826	10.1	7132	10.7	7331	11.7	6850	12.9	7060	15.7
Northern Ireland	2253	3.3	2343	3.5	2429	3.9	2599	4.9	2731	6.1
Smoking status										
Current smoker	4685	7.0	4500	6.8	4087	6.5	3305	6.2	2877	6.4
Past smoker	34297	50.9	34019	51.3	32258	51.3	27389	51.5	23119	51.3
Body mass index (kg/m^2)										
Missing data	5283	7.8	4588	6.9	3990	6.3	3209	6.0	2667	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	8197	12.2	8104	12.2	7421	11.8	6255	11.8	5564	12.3
Stroke risk factors										
Previous stroke/TIA	13136	19.5	12966	19.5	12312	19.6	10393	19.6	8986	19.9
Other arterial thromboembolism	281	0.4	267	0.4	243	0.4	207	0.4	182	0.4
Congestive heart failure	11970	17.8	11536	17.4	10780	17.2	9296	17.5	8272	18.3
Coronary artery disease	21158	31.4	20213	30.5	18691	29.7	15383	28.9	12892	28.6
Peripheral arterial disease	4136	6.1	3978	6	3671	5.8	2958	5.6	2491	5.5
Hypertension	65349	97.1	64557	97.3	61255	97.5	51872	97.6	44039	97.6
Diabetes mellitus	13949	20.7	13974	21.1	13564	21.6	11779	22.2	10222	22.7

	April 2012 (n=67327)		April 2013 (n=66364)		April 2014 (n=62840)		April 2015 (n=53150)		Jan 2016 (n=45105)	
	n	%	n	%	n	%	n	%	n	%
CHA2DS2-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 bleedings**	22136	32.9	22260	33.5	21770	34.6	18669	35.1	15889	35.2
Intracranial	1166	1.7	1223	1.8	1238	2.0	1039	2.0	897	2.0
Gastrointestinal	7755	11.5	7700	11.6	7575	12.1	6536	12.3	5677	12.6
Renal disease***	23367	34.7	23003	34.7	21391	34	17796	33.5	15061	33.4
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)	

Abbreviations: GP, general practitioner; NVAF, non-valvular atrial fibrillation; SD, standard deviation; TIA, transient ischaemic attack

* 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. Gynecological bleeds excluded.

*** Including any renal disease, chronic kidney disease stage 1-5

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 ≥ 2

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

Abbreviations: CI, confidence interval

Table 3. Factors associated with the prescription of aspirin or other antiplatelet for TE prevention in NVAF in April 2015 (vs. anticoagulation): results of the GEE model

	Antiplatelet therapy alone N=11,609		Treated with anticoagulant N= 33,413		OR (95% CI)	P-value
	n	%	N	%		
Patient age (years)						< .0001
< 65	890	7.7	2016	6.0	1.22 (1.10-1.35)	
65 to 74	2769	23.9	8780	26.3	Reference	
75 to 84	3842	33.1	14363	43.0	0.94 (0.87-1.02)	
≥ 85	4108	35.4	8254	24.7	1.72 (1.58-1.87)	
Country						0.001
England	8065	69.5	22909	68.6	Reference.	
Wales	1383	11.9	4524	13.5	0.80 (0.70-0.91)	
Scotland	1590	13.7	4231	12.7	1.06 (0.96-1.19)	
N. Ireland	571	4.9	1749	5.2	0.83 (0.72-0.97)	
Gender: male (reference = female)	5364	46.2	14580	43.6	0.87 (0.81-0.93)	<.0001
Time since NVAF diagnosis						<.0001
< 6 months	497	4.3	2121	6.3	Reference	
6 to 12 months	442	3.8	2175	6.5	0.96 (0.83-1.11)	
12 to 24 months	979	8.4	3886	11.6	1.24 (1.10-1.41)	
2 to 5 years since	3095	26.7	8496	25.4	1.89 (1.68-2.12)	
≥ 5 years	6596	56.8	16735	50.1	2.17 (1.93-2.44)	
Previous oral AC treatment						<.0001
No previous treatment	8093	69.7	21189	63.4	Reference	
NOAC only	87	0.7	411	1.2	0.61 (0.46-0.81)	
VKA and NOAC	76	0.7	490	1.5	0.37 (0.29-0.47)	
VKA only	3353	28.9	11323	33.9	0.65 (0.59-0.72)	
Previous stroke/TIA/arterial TE	2291	19.7	7341	22.0	0.83 (0.75-0.92)	0.0008
Congestive heart failure	1722	14.8	6685	20.0	0.61 (0.56-0.66)	<.0001
Previous coronary artery disease	4535	39.1	9636	28.8	1.60 (1.50--1.71)	<.0001

	Antiplatelet therapy alone N=11,609		Treated with anticoagulant N= 33,413		OR (95% CI)	P-value
	n	%	N	%		
Peripheral arterial disease	833	7.2	1887	5.6	1.20 (1.10-1.31)	0.0001
Hypertension	11308	97.4	32869	98.4	0.59 (0.51-0.69)	<.0001
CHA2DS2-VASc score						<.0001
2	1425	12.3	3444	10.3	Reference	
3	2408	20.7	7482	22.4	0.69 (0.63-0.76)	
4	3206	27.6	9656	28.9	0.56 (0.50-0.64)	
5	2306	19.9	6544	19.6	0.54 (0.46-0.64)	
≥6	2264	19.5	6287	18.9	0.52 (0.42-0.65)	
Previous bleed						<.0001
No bleed	7522	64.8	21577	64.6	Reference	
Intracranial bleed	346	3.0	404	1.2	3.02 (2.56-3.56)	
Gastrointestinal bleed	1430	12.3	4001	11.8	0.96 (0.90-1.02)	
Other bleed	2311	19.9	7473	22.4	0.82 (0.77-0.87)	
History of fall	3474	29.9	8211	24.6	1.14 (1.08-1.20)	<.0001
Renal disease	4106	35.4	11542	34.5	0.94 (0.90-0.99)	0.0131
Liver disease	102	0.9	214	0.6	1.32 (1.03-1.70)	0.0414
Number of comedications						<.0001
< 5	1448	12.5	6879	20.6	Reference	
5 to 9	5040	43.4	14825	44.4	1.71 (1.60-1.82)	
10 to 14	3169	27.3	7782	23.3	2.08 (1.93-2.26)	
15 or more	1952	16.8	3927	11.8	2.66 (2.43-2.91)	

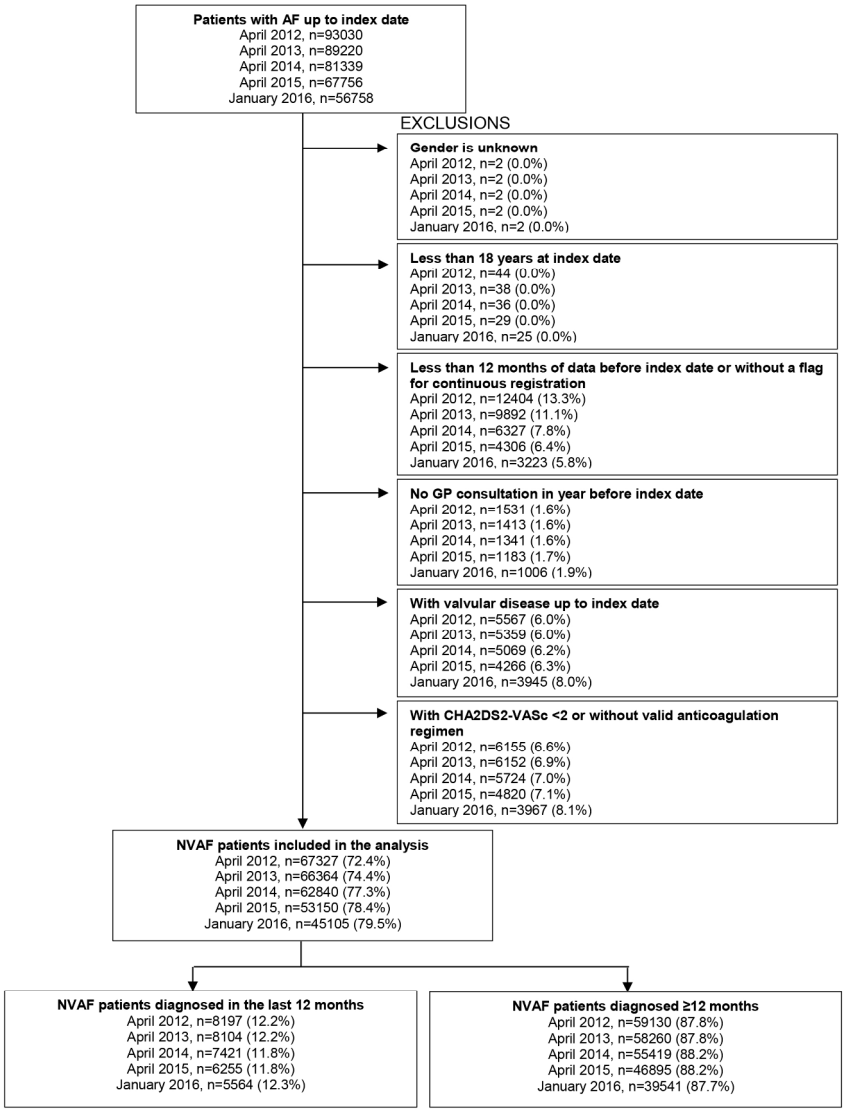
Abbreviations: CI, confidence interval; GEE, generalised estimating equations; VKA, vitamin K antagonist; OAC, oral anticoagulant; NVAF, non-valvular atrial fibrillation; TIA, transient ischaemic attack; TE, thromboembolism; OR, odds ratio; NOAC, novel oral anticoagulant.

Table 4. 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=8,128		Treated with anticoagulant N= 33,413		OR (95% CI)	P-value
	n	%	n	%		
Patient age (years)						<.0001
< 65	1299	16	2016	6.0	1.64 (1.47-1.83)	
65 to 74	2214	27.2	8780	26.3	Reference	
75 to 84	2367	29.1	14363	43.0	1.09 (0.99-1.20)	
≥ 85	2248	27.7	8254	24.7	1.86 (1.68-2.07)	
Gender: male (reference = female)	4450	54.7	14580	43.6	0.51 (0.46-0.56)	<.0001
Country						
England	5936	73.0	22909	68.6	Reference	<.0001
Wales	884	10.9	4524	13.5	0.80 (0.69-0.93)	
Scotland	1029	12.7	4231	12.7	1.09 (0.96-1.23)	
Northern Ireland	279	3.4	1749	5.2	0.69 (0.57-0.83)	
Time since NVAF diagnosis						<.0001
< 6 months	592	7.3	2121	6.3	Reference	
6 to 12 months	427	5.3	2175	6.5	0.71 (0.61-0.82)	
12 to 24 months	864	10.6	3886	11.6	0.82 (0.71-0.94)	
2 to 5 years	2086	25.7	8496	25.4	0.93 (0.82-1.06)	
≥ 5 years	4159	51.2	16735	50.1	1.07 (0.94-1.23)	
Previous OAC treatment						<.0001
No previous OAC	5137	63.2	21189	63.4	Reference	
NOAC only	189	2.3	411	1.2	1.82 (1.36-2.43)	
VKA and NOAC	159	2.0	490	1.5	1.50 (1.23-1.84)	
VKA only	2643	32.5	11323	33.9	0.97 (0.88-1.07)	
Previous stroke/TIA/ arterial TE	968	11.9	7341	22.0	0.55 (0.48-0.64)	<.0001
Congestive heart failure	889	10.9	6685	20.0	0.76 (0.69-0.84)	<.0001

Parameter	No antithrombotic therapy N=8,128		Treated with anticoagulant N= 33,413		OR (95% CI)	P-value
	n	%	n	%		
Previous coronary artery disease	1212	14.9	9636	28.8	0.76 (0.70-0.84)	<.0001
Hypertension	7695	94.7	32869	98.4	0.62 (0.53-0.72)	<.0001
CHA2DS2-VASc score						<.0001
2	2212	27.2	3444	10.3	Reference	
3	2034	25	7482	22.4	0.48 (0.43-0.54)	
4	2057	25.3	9656	28.9	0.33 (0.28-0.39)	
5	987	12.1	6544	19.6	0.28 (0.22-0.35)	
≥6	838	10.27	6287	18.9	0.27 (0.20-0.36)	
Previous bleed						<.0001
No bleed	5382	66.2	21577	64.6	Reference	
IC bleed	289	3.6	404	1.2	8.03 (6.43-10.02)	
GI bleed	1016	12.5	4001	11.8	1.24 (1.14-1.35)	
Other bleed	1441	17.7	7473	22.4	0.91 (0.85-0.97)	
History of peptic ulcer	465	5.7	1743	5.2	1.36 (1.21-1.52)	<.0001
History of anaemia	227	2.8	880	2.6	1.44 (1.24-1.67)	<.0001
History of fall	2097	25.8	8211	24.6	1.20 (1.13-1.28)	<.0001
Renal disease	2148	26.4	11542	34.5	0.90 (0.84-0.96)	0.0016
Liver disease	109	1.3	214	0.6	2.39 (1.87-3.05)	<.0001
Active cancer	455	3.9	1367	4.1	1.19 (1.06-1.35)	0.0053
Number of co-medications						<.0001
< 5	3384	41.6	6879	20.6	Reference	
5 to 9	2791	34.3	14825	44.4	0.49 (0.45-0.52)	
10 to 14	1271	15.6	7782	23.3	0.46 (0.43-0.50)	
≥15	682	8.4	3927	11.8	0.53 (0.48-0.59)	

Abbreviations: CI, confidence interval; GEE, generalised estimating equations; VKA, vitamin K antagonist; OAC, oral anticoagulant; NVAF, non-valvular atrial fibrillation; TIA, transient ischaemic attack; TE, thromboembolism; OR, odds ratio; NOAC, novel oral anticoagulant



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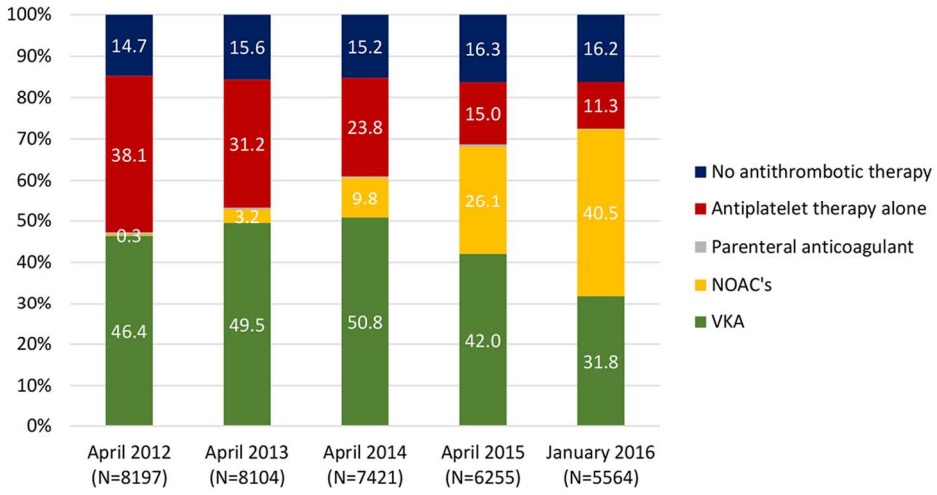

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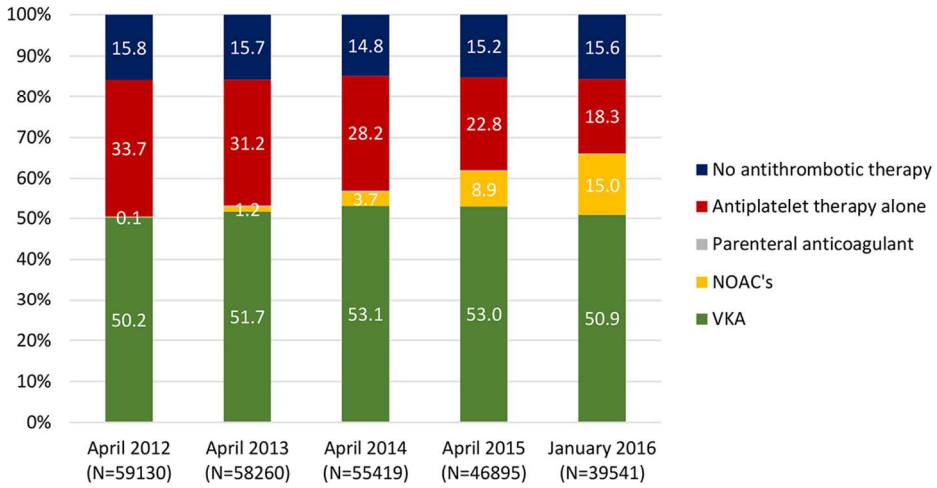

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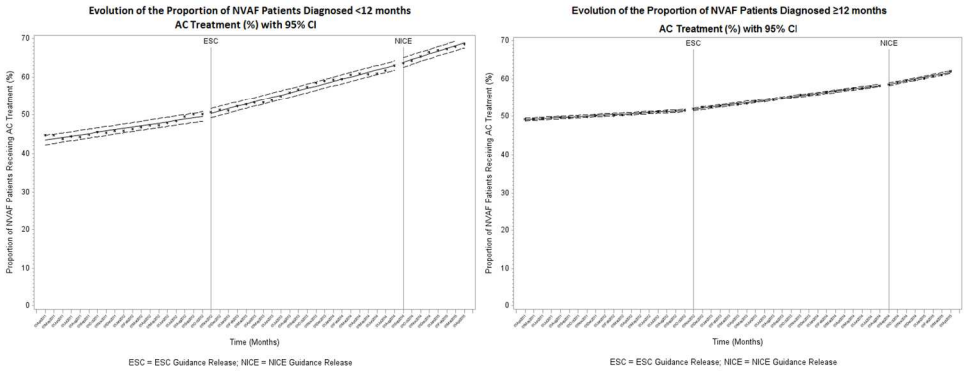

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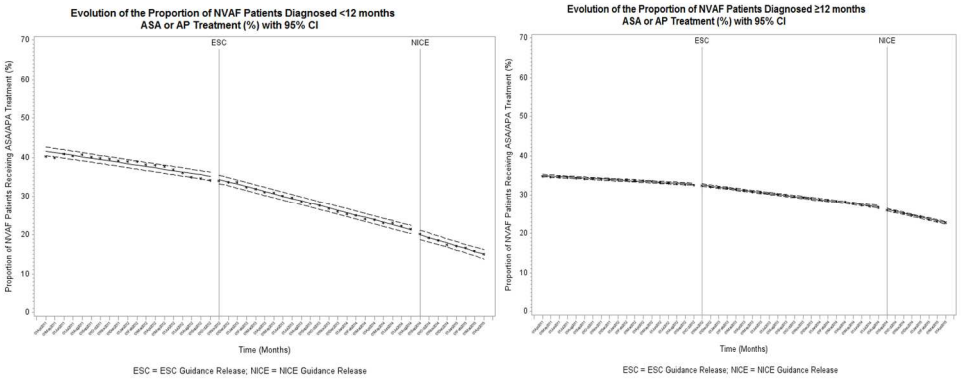

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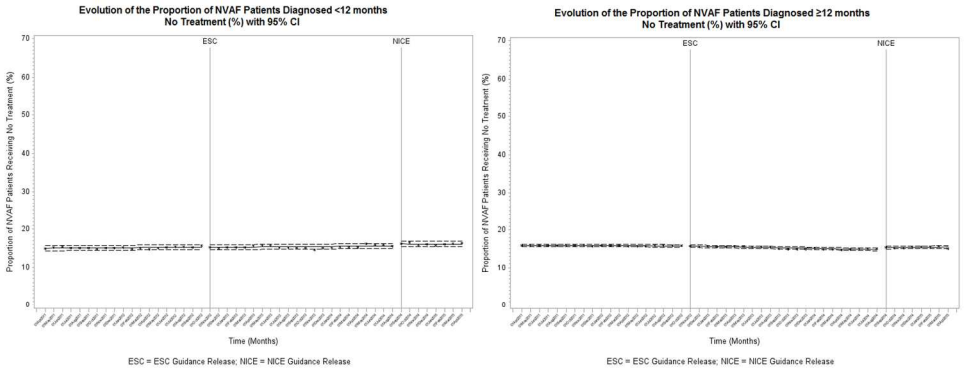

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DATA SUPPLEMENT

Table s1. READ code descriptions

G11..00	Mitral valve diseases
G540.15	Mitral valve prolapse
G110.00	Mitral stenosis
G540.00	Mitral valve incompetence
G541.00	Aortic valve disorders
G540000	Mitral incompetence, non-rheumatic
G130.00	Mitral and aortic stenosis
G13..00	Diseases of mitral and aortic valves
G541400	Aortic valve stenosis with insufficiency
G131.14	Mitral stenosis and aortic regurgitation
G544200	Combined disorders of mitral, aortic and tricuspid valves
G541z00	Aortic valve disorders NOS
G544100	Disorders of both mitral and tricuspid valves
G540z00	Mitral valve disorders NOS
G113.00	Nonrheumatic mitral valve stenosis
G13z.00	Mitral and aortic valve disease NOS
G11z.00	Mitral valve disease NOS
G133.00	Mitral and aortic incompetence
G132.12	Mitral incompetence and aortic stenosis
G540200	Mitral valve prolapse
G132.00	Mitral insufficiency and aortic stenosis
G132.13	Mitral regurgitation and aortic stenosis
G540100	Mitral incompetence, cause unspecified
G540300	Mitral valve leaf prolapse
G544.00	Multiple valve diseases
G540.12	Mitral valve insufficiency
G112.13	Mitral stenosis with regurgitation
G112.00	Mitral stenosis with insufficiency
Gyu5600	[X]Other aortic valve disorders
G131.00	Mitral stenosis and aortic insufficiency
G12z.00	Rheumatic aortic valve disease NOS
G112.12	Mitral stenosis with incompetence
Gyu1000	[X]Other mitral valve diseases
P65..00	Congenital mitral stenosis

G544X00	Multiple valve disease, unspecified
G114.00	Ruptured mitral valve cusp
G131.13	Mitral stenosis and aortic incompetence
P66..00	Congenital mitral insufficiency
P652.00	Parachute deformity of the mitral valve
G13y.00	Multiple mitral and aortic valve involvement
Gyu5A00	[X]Aortic valve disorders in diseases classified elsewhere
P650.00	Congenital mitral stenosis, unspecified
G133.11	Mitral and aortic insufficiency
Gyu5500	[X]Other nonrheumatic mitral valve disorders
P65z.00	Congenital mitral stenosis NOS
Gyu5D00	[X]Multiple valve disorders/diseases CE
READ Codes for prosthetic valve description	
7911.12	Replacement of aortic valve
P641.00	Bicuspid aortic valve
7910300	Replacement of mitral valve NEC
7910.12	Replacement of mitral valve
7910.12	Replacement of mitral valve
7914300	Replacement of valve of heart NEC
7914200	Prosthetic replacement of valve of heart NEC
7910.00	Plastic repair of mitral valve
7911.00	Plastic repair of aortic valve
7911300	Replacement of aortic valve NEC
7915000	Revision of plastic repair of mitral valve
7916000	Open mitral valvotomy
7917000	Closed mitral valvotomy
7910200	Prosthetic replacement of mitral valve
7910200	Prosthetic replacement of mitral valve
7910400	Mitral valvuloplasty NEC
ZV43300	[V]Has artificial heart valve
7914.11	Replacement of unspecified valve of heart
7910211	Bjork-Shiley prosthetic replacement of mitral valve
7911200	Prosthetic replacement of aortic valve
7910.11	Mitral valvuloplasty
7914212	Starr prosthetic replacement of valve of heart
7911100	Xenograft replacement of aortic valve

7911y00	Other specified plastic repair of aortic valve
ZV45H00	[V]Presence of prosthetic heart valve
7910z00	Plastic repair of mitral valve NOS
7911000	Allograft replacement of aortic valve
7915100	Revision of plastic repair of aortic valve
7914211	Edwards prosthetic replacement of valve of heart
TB01200	Implant of heart valve prosthesis + complication, no blame
7910213	Carpentier prosthetic replacement of mitral valve
7910100	Xenograft replacement of mitral valve
7919000	Percutaneous transluminal mitral valvotomy
7911z00	Plastic repair of aortic valve NOS
7910212	Bjork-Shiley prosthetic replacement of mitral valve
7910y00	Other specified plastic repair of mitral valve
SP00200	Mechanical complication of heart valve prosthesis
SyuK611	[X] Embolism from prosthetic heart valve
790D700	Replacement of valved cardiac conduit
7914100	Xenograft replacement of valve of heart NEC
7914000	Allograft replacement of valve of heart NEC
ZVu6e00	[X]Presence of other heart valve replacement
7910214	Edwards prosthetic replacement of mitral valve
7910411	Mitral valve repair NEC
7911411	Aortic valve repair NEC
7910000	Allograft replacement of mitral valve
7911600	Transluminal aortic valve implantation
7911500	Transapical aortic valve implantation
7914600	Replacement of truncal valve
7918000	Annuloplasty of mitral valve

Table s2. Proportion of patients with NVAF treated in April 2012, 2013, 2014, and 2015 in the UK, according to duration of diagnosis

	April 2012 % [95% CI]	April 2013 % [95% CI]	April 2014 % [95% CI]	April 2015 % [95% CI]	January 2016 % [95% CI]
Diagnosed < 12 months					
Anticoagulation treatment	**47.2 [46.2-48.3]**	**53.2 [52.1-54.2]**	**61.0 [59.9-62.0]**	**68.7 [67.6-69.8]**	**72.5 [71.3-73.7]**
VKA	46.4 [45.4-47.4]	49.5 [48.5-50.6]	50.8 [49.7-51.9]	42.0 [40.8-43.1]	31.8 [30.6-33.0]
Apixaban	-	-	1.7 [1.5-2.0]	8.8 [8.1-9.5]	16.6 [15.6-17.5]
Rivaroxaban	-	1.2 [1.0-1.5]	5.5 [5.0-6.0]	14.5 [13.7-15.3]	21.5 [20.4-22.6]
Dabigatran	0.3 [0.2-0.4]	2.0 [1.7-2.3]	2.6 [2.3-2.9]	2.8 [2.5-3.2]	2.4 [2.0-2.8]
Parenteral anticoagulant	0.5 [0.4-0.6]	0.5 [0.3-0.6]	0.4 [0.2-0.5]	0.6 [0.4-0.8]	0.2 [0.1-0.4]
Antiplatelet therapy alone	**38.1 [37-39.1]**	**31.2 [30.2-32.1]**	**23.8 [22.9-24.8]**	**15 [14.2-15.9]**	**11.3 [10.5-12.1]**
No antithrombotic therapy	**14.7 [14-15.4]**	**15.6 [14.9-16.4]**	**15.2 [14.4-16]**	**16.3 [15.4-17.2]**	**16.2 [15.2-17.1]**
Diagnosed ≥ 12 months					
Anticoagulation treatment	**50.6 [50.2-51.0]**	**53.2 [52.8-53.5]**	**57.0 [56.6-57.4]**	**62.1 [61.7-62.5]**	**66.1 [65.6-66.6]**
VKA	50.2 [49.8-50.6]	51.7 [51.3-52.1]	53.1 [52.7-53.5]	53.0 [52.5-53.4]	50.9 [50.4-51.4]
Apixaban	-	-	0.4 [0.3-0.4]	2.0 [1.9-2.1]	4.5 [4.3-4.7]
Rivaroxaban	-	0.5 [0.4-0.5]	1.9 [1.8-2.0]	4.9 [4.7-5.1]	8.3 [8.0-8.6]
Dabigatran	0.1 [0.1-0.1]	0.7 [0.7-0.8]	1.4 [1.3-1.5]	2.0 [1.9-2.1]	2.2 [2.1-2.4]
Parenteral anticoagulant	0.2 [0.2-0.3]	0.3 [0.2-0.3]	0.3 [0.2-0.3]	0.2 [0.2-0.3]	0.2 [0.2-0.3]
Antiplatelet therapy alone	**33.7 [33.3-34.0]**	**31.2 [30.8-31.5]**	**28.2 [27.8-28.5]**	**22.8 [22.4-23.1]**	**18.3 [17.9-18.7]**
No antithrombotic therapy	**15.8 [15.5-16.0]**	**15.7 [15.4-16.0]**	**14.8 [14.5-15.1]**	**15.2 [14.8-15.5]**	**15.6 [15.3-16.0]**

Abbreviations: CI, confidence interval; VKA, vitamin K antagonists

Table s3. Proportion of patients with NVAF treated in April 2012, 2013, 2014, and 2015 in the UK,. according to country of residence

	April 2012 % [95% CI]	April 2013 % [95% CI]	April 2014 % [95% CI]	April 2015 % [95% CI]	January 2016 % [95% CI]
England					
Anticoagulation treatment	**49.6 [49.2-50]**	**52.4 [52-52.9]**	**56.9 [56.5-57.4]**	**62.1 [61.6-62.5]**	**66.5 [66.0-67.1]**
VKA	49.2 [48.8-49.6]	50.8 [50.4-51.2]	52.4 [51.9-52.8]	51.3 [50.8-51.8]	47.9 [47.4-48.5]
Apixaban	-	-	0.4 [0.4-0.5]	2.3 [2.2-2.5]	5.0 [4.8-5.3]
Rivaroxaban	-	0.5 [0.4-0.5]	2.1 [2.0-2.2]	5.7 [5.5-5.9]	10.7 [10.3-11.0]
Dabigatran	0.1 [0.1-0.1]	0.9 [0.8-1.0]	1.7 [1.6-1.8]	2.4 [2.3-2.6]	2.6 [2.4-2.8]
Parenteral anticoagulant	0.3 [0.2-0.3]	0.3 [0.2-0.3]	0.3 [0.3-0.4]	0.3 [0.3-0.4]	0.2 [0.2-0.3]
Antiplatelet therapy alone	**33.9 [33.5-34.3]**	**30.9 [30.6-31.3]**	**27.5 [27.1-27.9]**	**21.9 [21.4-22.3]**	**17.0 [16.5-17.4]**
No antithrombotic therapy	**16.5 [16.2-16.8]**	**16.6 [16.3-16.9]**	**15.6 [15.3-15.9]**	**16.1 [15.7-16.4]**	**16.5 [16.1-17.0]**
Scotland					
Anticoagulation treatment	**48.8 [47.7-49.9]**	**51.9 [50.8-53]**	**55.5 [54.4-56.6]**	**61.8 [60.7-62.9]**	**64.3 [63.2-65.4]**
VKA	48.2 [47.1-49.3]	49.2 [48.1-50.3]	49.1 [48.0-50.2]	48.4 [47.2-49.5]	45.2 [44-46.3]
Apixaban	-	-	0.5 [0.3-0.6]	2.7 [2.3-3.0]	6.6 [6.0-7.2]
Rivaroxaban	-	1.8 [1.5-2.0]	5.0 [4.5-5.4]	9.8 [9.1-10.5]	11.6 [10.8-12.3]
Dabigatran	0.4 [0.2-0.5]	0.5 [0.4-0.7]	0.7 [0.5-0.8]	0.7 [0.5-0.8]	0.8 [0.6-1.0]
Parenteral anticoagulant	0.2 [0.1-0.3]	0.4 [0.2-0.5]	0.3 [0.2-0.4]	0.2 [0.1-0.3]	0.1 [0.1-0.2]
Antiplatelet therapy alone	**37 [35.9-38.1]**	**33.6 [32.6-34.7]**	**29.6 [28.6-30.6]**	**23.2 [22.3-24.2]**	**19.9 [19.0-20.8]**
No antithrombotic therapy	**14.2 [13.4-15.0]**	**14.5 [13.7-15.3]**	**14.9 [14.2-15.7]**	**15 [14.2-15.8]**	**15.8 [14.9-16.6]**
Wales					
Anticoagulation treatment	**55.1 [54.0-56.2]**	**58.7 [57.7-59.8]**	**61.7 [60.6-62.7]**	**66.6 [65.5-67.7]**	**69.1 [68.0-70.2]**
VKA	54.8 [53.7-55.9]	57.6 [56.5-58.7]	59.1 [58.0-60.1]	59.3 [58.1-60.4]	57.6 [56.5-58.8]
Apixaban	-	0.0 [0.0-0.1]	0.3 [0.2-0.4]	2.2 [1.9-2.5]	3.9 [3.4-4.3]
Rivaroxaban	-	0.1 [0.0-0.2]	0.9 [0.7-1.1]	3.2 [2.8-3.6]	5.1 [4.6-5.6]
Dabigatran	0.0 [0.0-0.1]	0.9 [0.6-1.1]	1.3 [1.1-1.5]	1.9 [1.6-2.2]	2.3 [2.0-2.7]
Parenteral anticoagulant	0.2 [0.1-0.3]	0.2 [0.1-0.3]	0.1 [0.1-0.2]	0.1 [0.0-0.1]	0.2 [0.1-0.2]
Antiplatelet therapy alone	**32.5 [31.5-33.6]**	**29.4 [28.4-30.4]**	**26.7 [25.8-27.7]**	**20.4 [19.4-21.3]**	**16.8 [15.9-17.7]**
No antithrombotic therapy	**12.4 [11.6-13.1]**	**11.9 [11.2-12.6]**	**11.6 [10.9-12.3]**	**13.0 [12.2-13.8]**	**14.1 [13.3-14.9]**
Northern Ireland					
Anticoagulation treatment	**51.5 [49.6-53.5]**	**55 [53.0-56.9]**	**60.8 [59.0-62.7]**	**67.3 [65.6-69.0]**	**71.9 [70.2-73.6]**
VKA	50.7 [48.7-52.7]	52.4 [50.4-54.3]	51.5 [49.6-53.4]	46 [44.2-47.9]	39.7 [37.9-41.6]
Apixaban	-	0.1 [0.0-0.2]	3.1 [2.4-3.7]	11.1 [10.0-12.3]	19.1 [17.6-20.6]
Rivaroxaban	-	0.4 [0.1-0.6]	3.5 [2.8-4.2]	7.5 [6.5-8.4]	10.7 [9.5-11.8]
Dabigatran	0.5 [0.2-0.8)	1.6 [1.1-2.1]	2.5 [1.9-3.1]	2.3 [1.8-2.9]	2.1 [1.6-2.7]

Management of NVAF in Europe and the UK

	April 2012 % [95% CI]	April 2013 % [95% CI]	April 2014 % [95% CI]	April 2015 % [95% CI]	January 2016 % [95% CI]
Parenteral anticoagulant	0.3 [0.1-0.5]	0.6 [0.3-0.8]	0.2 [0.1-0.4]	0.3 [0.1-0.6]	0.3 [0.1-0.5]
Antiplatelet therapy alone	**37.9 [35.9-39.8]**	**34.1 [32.2-35.9]**	**28.2 [26.4-29.9]**	**22 [20.4-23.5]**	**17.2 [15.8-18.6]**
No antithrombotic therapy	**10.6 [9.4-11.8]**	**11 [9.8-12.2]**	**11.0 [9.8-12.2]**	**10.7 [9.6-11.9]**	**10.9 [9.8-12.1]**

Abbreviations: CI, confidence interval; VKA, vitamin K antagonists

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any pre-specified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4-5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4-5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	n/a
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4-5
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	n/a
		(*c*) Explain how missing data were addressed	n/a
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	10
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	20
		(b) Give reasons for non-participation at each stage	20
		(c) Consider use of a flow diagram	20
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	16
		(b) Indicate number of participants with missing data for each variable of interest	16
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	n/a
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	n/a
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	n/a
		Cross-sectional study—Report numbers of outcome events or summary measures	6, 16, 17-19
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	17
		(*b*) Report category boundaries when continuous variables were categorized	18-19
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10
Discussion			
Key results	18	Summarise key results with reference to study objectives	8
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9-10
Generalisability	21	Discuss the generalisability (external validity) of the study results	10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.