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TRENDS IN THE PHARMACOLOGICAL MANAGEMENT OF ATRIAL FIBRILLATION IN UK GENERAL PRACTICE 2008-2018

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ABSTRACT

Objective: The pharmacological management of atrial fibrillation (AF) comprises anticoagulation, for stroke prophylaxis; and rate or rhythm control drugs, to alleviate symptoms and prevent heart failure. The aim of this study was to investigate trends in the proportion of patients with AF prescribed pharmacological therapies in the UK between 2008 and 2018.

Methods: Eleven sequential cross-sectional analyses were performed yearly from 2008 to 2018. Data were derived from an anonymised UK primary care database. Outcomes were the proportion of patients with AF prescribed anticoagulants, rhythm and rate control drugs in the whole cohort, those at high risk of stroke, and those with co-existing heart failure.

Results: Between 2008 and 2018, the proportion of patients prescribed anticoagulants increased from 45.3% (95% CI 45.0-45.7%) to 71.1% (95% CI 70.7-71.5%) driven by increased prescription of non-vitamin K antagonist anticoagulants (NOACs). The proportion of patients prescribed rate control drugs remained constant between 2008 and 2018 (69.3% (95% CI 68.9-69.6%) to 71.6% (95% CI 71.2%-71.9%)). The proportion of patients prescribed rhythm control therapy by GPs decreased from 9.5% (95% CI 9.3-9.7%) to 5.4% (95% CI 5.2-5.6%).

Conclusions: There has been an increase in the proportion of patients with AF appropriately prescribed anticoagulants following NICE and ESC guidelines which correlates with improvements in mortality and stroke outcomes. Beta blockers appear increasingly favoured over digoxin for rate control. There has been a steady decline in GP prescribing rates for rhythm control drugs, possibly related to concerns over efficacy and safety and increased availability of AF ablation.

KEY MESSAGES

What is already known about this subject?

Appropriate pharmacological management of atrial fibrillation (AF) can prevent AF-related stroke and heart failure and alleviate symptoms associated with a poorly controlled ventricular rate. Previous UK studies have shown under-treatment of moderate and high risk patients with AF, as well as over-treatment of those at low risk, although it has been demonstrated that anticoagulants are being prescribed more appropriately in recent years. Patterns of prescribing over time, broken down by individual pharmaceutical agent have not been recently described for the UK setting.

What does this study add?

There has been an increase in the proportion of patients with AF appropriately prescribed anticoagulants over the past decade, driven by an increase in the prescription of non-vitamin K antagonist oral anticoagulants (NOACs) and associated with a decline in the prescription of warfarin. Rates of prescribing of rate control in AF have remained constant between 2008 and 2018. There has been an increased use of beta blockers, reflecting increased compliance with guidance. Rhythm control drugs are prescribed less frequently than a decade ago in primary care.

How might this impact on clinical practice?

Over the past ten years, pharmacological treatment of AF in primary care has improved. However, there remains some scope for bringing the management of AF in line with guidance and evidence.

INTRODUCTION

Atrial fibrillation (AF) is a common cardiac arrhythmia estimated to have affected almost 1.5 million people in England in 2019.[1] The prevalence of AF is increasing,[2] thought to be related to factors such as the ageing population and the increasing prevalence of risk factors (such as obesity, hypertension and diabetes).[3] AF increases the risk of stroke and can lead to left ventricular dysfunction and heart failure.[4] The aims of treatment are to prevent AF-related stroke, alleviate symptoms and to manage cardiovascular risk factors.[5,6,7]

AF has a high burden on patients, their caregivers and health services. Symptoms such as palpitations, fatigue and shortness of breath can be debilitating and complications, such as heart failure and ischaemic stroke, are associated with long term morbidity and mortality. AF patients report lower health-related quality of life than the general population. AF and its complications, in particular stroke, can impact on ability to perform activities of daily living, meaning patients are reliant on caregivers for assistance.[8] At least one fifth of all strokes are related to AF.[9] AF-related strokes can often be more severe and disabling and are associated with a 70% increase in in-hospital mortality, a 40% reduction in likelihood of discharge to the patient's own home and a 20% increase in the length of stay.[10] AF accounts for 0.9-2.4% of the UK healthcare budget, with hospital costs accounting for the majority of this. The mean annual cost per patient of AF-related ischaemic stroke and embolic events were £22423-23345 and £13634-13720 respectively in 2008-2009. Anticoagulation can prevent AF-related strokes in up to two thirds of patients.[8] Therefore, optimising AF treatment has the potential to improve the quality of life of patients, reduce the burden on caregivers and reduce healthcare costs.

The National Institute for Health and Care Excellence (NICE) and other European guidelines recommend anticoagulant prophylaxis for patients with AF at risk of stroke as determined by a CHA_2DS_2-VASc score ≥2.[5,7,11] Warfarin was the mainstay of anticoagulation treatment in AF until the introduction of non-vitamin K antagonist oral anticoagulants (NOACs), also referred to as direct acting oral anticoagulants (DOACs) (apixaban, dabigatran, edoxaban and rivaroxaban). NOACs were approved for use in the UK from 2008.[12] Up until 2020, NICE gave warfarin and NOACs equal weighting as options for anticoagulation,[5] however, updated guidelines, expected to be published in 2021, are likely to recommend NOACs as the first line choice over warfarin.[13] The European Society of Cardiology have also recommended NOACs as first line in 2020.[7]

For most patients with AF being managed in primary care, rate control treatment is recommended as first line.[14] The aim of rate control therapy is to regulate the heart rate during AF, reduce symptoms and prevent heart failure.[6]

Rhythm control therapies can be considered if adequate rate control cannot be achieved, or if symptoms persist despite optimum rate control.[5] The aim of rhythm control is to restore and maintain sinus rhythm.[6]

In the past, an under-treatment of moderate and high risk patients with AF had been noted as well as over-treatment of those at low risk, although it has since been demonstrated that anticoagulants are being prescribed increasingly more appropriately in recent years.[2] Patterns of prescribing over time, broken down by individual pharmaceutical agent have not been recently described for the UK setting.

The purpose of this study was to determine the proportion of patients in the UK with AF prescribed anticoagulant treatment, rate control therapy and rhythm control therapy and examine trends in the use of individual pharmaceutical agents for the management of AF between 2008 and 2018, stratifying these patients by stroke risk and presence or absence of heart failure.

METHODS

Data Source

Data for this analysis was obtained from IQVIA Medical Research Data (IMRD), an anonymised database of electronic primary care records from general practices in the UK using Vision software. All participating practices contribute coded data on patient characteristics, prescriptions, consultations, diagnoses and primary care investigations. Previous validation studies have demonstrated that IMRD is largely representative of the UK population in terms of demographics and morbidity prevalence.[15] Symptoms, examinations, and diagnoses in IMRD are recorded using a hierarchical clinical coding system called Read codes.[16] As a data quality control measure, practices were eligible for inclusion in study from 12 months after the latest of practice acceptable mortality recording date (AMR)[17] or Vision installation date.

The data extraction and cohort selection was facilitated using the data extraction for epidemiological research (DExtER) tool.[18]

All analyses were conducted using Stata IC version 14.2.

Study design

Cross-sectional analyses were performed on 1st January (the census date) each year from 2008 to 2018. To be eligible for inclusion, patients were required to be adults with a record of AF prior to the census date, with no clinical coding indicating 'AF resolved' recorded after the last AF code and prior to the census date. Patients with eGFR ≤30mL/min were excluded due to the caution advised with prescribing NOACs for patients with a low creatinine clearance. As AF is recorded within the Quality Outcomes Framework (QOF), it is anticipated that coding will be accurate.[19]

Definitions of variables

AF diagnosis was defined by the presence of a clinical (Read) code for atrial fibrillation or atrial flutter at any time prior to the census date, excluding patients with a more recent clinical code prior to the census date indicating that AF had resolved.

Current anticoagulant treatment was defined by a record of a prescription for any anticoagulant medication (warfarin, or non-vitamin K antagonist oral anticoagulants (NOACs) within 90 days prior to the census date. Current rate control treatment was defined as a record of prescription for any rate control medication (beta blockers; rate controlling calcium channel blockers (verapamil or diltiazem); or digoxin) within 90 days prior to the census date. Current rhythm control treatment was defined as a record of prescription for any rhythm control medication (flecainide acetate, amiodarone hydrochloride, dronedarone or propafenone hydrochloride) within 90 days prior to the census date. Sotalol was considered a rate control medication and not rhythm control for the purpose of this analysis.

CHA_2DS_2-VASc scores[20] were calculated by adding one point each for a history of congestive heart failure, hypertension, diabetes, vascular disease, age 65-74 years and female sex, and two points for age ≥75 years and history of stroke, transient ischaemic attack (TIA) or thromboembolism. History of most comorbidities was defined by a clinical code recorded prior to the census date, excluding diabetic patients with a later record indicating diabetes resolved.

See supplementary appendix for clinical (Read) code list.

Missing data

The absence of a clinical code was taken to indicate that the diagnosis was absent; and the absence of a recorded prescription was taken to indicate that the medication was not prescribed. In describing baseline patient characteristics, a missing category was created for Townsend quintile and the proportion with no record of ethnicity was described.

Statistical analysis

Proportions of patients prescribed individual anticoagulants, rhythm control and rate control drugs within the 90 days prior to the census date were calculated for each year of the study. 95% confidence intervals for proportions were calculated using the normal approximation method. In the primary analysis, patients were stratified as low (CHA_2DS_2-VASc <2) or high stroke risk (CHA_2DS_2-VASc ≥2). Trends over time were plotted. In sensitivity analysis, prescribing patterns in patients with and without heart failure were examined.

Patient and public involvement

No patients were actively involved in setting the research question, outcome measures, study design, results interpretation or write up of the results.

RESULTS

The records of 224506 individual patients with AF were included in the analysis across the 11 census dates. All 772 practices for which data were available during the study period were included. Demographic characteristics are displayed in table 1. The mean age of patients changed little between 2008 and 2018. 55.1% of the cohort were male in 2008, increasing to 59.1% in 2018. A greater proportion of patients were in the lowest (least deprived) than the highest (most deprived) Townsend quintile (although the proportion of patients for whom Townsend score was missing increased from 10.7% in 2008 to 20.3% in 2018). The proportion high risk patients according to CHA_2DS_2-VASc changed little between 2008 and 2018.

Table 1: Demographic characteristics of patients with atrial fibrillation 2008-2018

Year	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
Population (n)	65039	71700	74010	75411	78693	81447	78854	75720	64945	59307	53245
Age (mean (SD))	74.4 (11.6)	74.4 (11.6)	74.5 (11.6)	74.6 (11.6)	74.6 (11.7)	74.5 (11.7)	74.5 (11.7)	74.5 (11.7)	74.3 (11.7)	74.3 (11.7)	74.4 (11.8)
Male sex, n (%)	35873 (55.2)	39806 (55.5)	41437 (56.0)	42512 (56.4)	44534 (56.6)	46477 (57.1)	45407 (57.6)	43881 (58.0)	38003 (58.5)	34878 (58.8)	31487 (59.1)
Ethnicity, n (%)											
White	24860 (38.2)	30158 (42.1)	32865 (44.4)	34937 (46.3)	37044 (47.1)	39808 (48.9)	39045 (49.6)	36969 (48.8)	31286 (48.2)	28529 (48.1)	24818 (46.6)
South Asian	230 (0.4)	284 (0.4)	314 (0.4)	353 (0.5)	394 (0.5)	445 (0.6)	460 (0.6)	397 (0.5)	284 (0.4)	274 (0.5)	248 (0.5)
Black	122 (0.2)	144 (0.2)	166 (0.2)	180 (0.2)	200 (0.3)	213 (0.3)	207 (0.3)	174 (0.2)	139 (0.2)	140 (0.2)	113(0.2)
Mixed	66 (0.1)	83 (0.1)	96 (0.1)	115 (0.2)	156 (0.2)	190 (0.2)	210 (0.3)	175 (0.2)	139 (0.2)	134 (0.2)	129 (0.2)
Other	34 (0.1)	37 (0.1)	47 (0.1)	51 (0.1)	56 (0.1)	64 (0.1)	71 (0.1)	66 (0.1)	60 (0.1)	51 (0.1)	58 (0.1)
Ethnicity not recorded	39727 (61.1)	40994 (57.2)	40522 (54.8)	39775 (52.7)	40843 (51.9)	40727 (50.0)	38861 (49.3)	37939 (50.1)	33037 (50.9)	30179 (50.9)	27245 (52.4)
Townsend Score, n (%)											
1 (Least Deprived)	15,440 (23.7)	16,997 (23.7)	17,950 (24.3)	18,350 (24.3)	18,949 (24.1)	19,171 (23.5)	18,304 (23.2)	17,108 (22.6)	13,461 (20.7)	11,796 (19.9)	9,857 (18.5)
2	13,766 (21.2)	15,481 (21.6)	16,080 (21.7)	16,399 (21.8)	16,853 (21.4)	17,103 (21.0)	16,619 (21.1)	16,041 (21.2)	13,436 (20.7)	11,773 (19.9)	10,348 (19.4)
3	12,286 (18.9)	13,633 (19.0)	13,978 (18.9)	14,231 (18.9)	14,796 (18.8)	15,313 (18.8)	14,764 (18.7)	14,127 (18.7)	11,987 (18.5)	10,699 (18.0)	9,564 (18.0)
4	10,062 (15.5)	11,121 (15.5)	11,224 (15.2)	11,318 (15.0)	11,839 (15.0)	12,416 (15.2)	11,873 (15.1)	11,368 (15.0)	9,805 (15.1)	8,755 (14.8)	7,649 (14.4)
5 (Most Deprived)	6,512 (10.0)	7,189 (10.0)	7,297 (9.9)	7,312 (9.7)	7,528 (9.6)	8,017 (9.8)	7,529 (9.6)	7,127 (9.4)	6,288 (9.7)	5,868 (9.9)	5,043 (9.5)
Missing	6,973 (10.7)	7,279 (10.2)	7,481 (10.1)	7,801 (10.3)	8,728 (11.1)	9,427 (11.6)	9,765 (12.4)	9,949 (13.1)	9,968 (15.4)	10,416 (17.6)	10,784 (20.3)
High CHA_2DS_2-VASc risk score (≥2), n (%)	54140 (83.2)	59790 (83.4)	61817 (83.5)	63026 (83.6)	65855 (83.7)	68146 (83.7)	65925 (83.6)	63180 (83.4)	54208 (83.5)	49360 (83.2)	44249 (83.1)
Heart failure diagnosis, n (%)	11938 (18.4)	12719 (17.7)	12859 (17.4)	13009 (17.3)	13378 (17.0)	13638 (16.7)	13312 (16.9)	12963 (17.1)	11550 (17.8)	10547 (17.8)	9353 (17.6)
Comorbidities, n (%)											
Hypertension	37318 (57.4)	41787 (58.3)	43436 (58.7)	44511 (59.0)	46487 (59.1)	48204 (59.2)	46423 (58.9)	44221 (58.4)	37979 (58.5)	34643 (58.4)	30732 (57.7)

Diabetes Mellitus	10276 (15.8)	11818 (16.5)	12562 (17.0)	13180 (17.5)	13937 (17.7)	14712 (18.1)	14725 (18.7)	14334 (18.9)	12712 (19.6)	11836 (20.0)	10643 (20.0)
Vascular Disease*	12031 (18.5)	13041 (18.2)	13131 (17.7)	13164 (17.5)	13439 (17.1)	13570 (16.7)	12886 (16.3)	12121 (16.0)	10296 (15.9)	9195 (15.5)	8218 (15.4)
Stroke/TIA/ Thromboembolic Disease**	11589 (17.8)	12888 (18.0)	13263 (17.9)	13607 (18.0)	14244 (18.1)	14724 (18.1)	14226 (18.0)	13703 (18.1)	11762 (18.1)	10634 (17.9)	9441 (17.7)

* Defined as coronary artery disease, peripheral artery disease, previous MI, cerebrovascular disease (excluding stroke and TIA). **Defined as thromboembolic disease of an artery.

Prescription of anticoagulants

Between 2008 and 2018, the proportion of patients with AF prescribed anticoagulants increased from 45.3 (95% CI 45.0-45.7%) to 71.1% (95% CI 70.7-71.5%). NOACs were first prescribed in the study population in 2010, for 2 out of 85526 patients. This proportion has risen steadily to 34.4% (95% CI 34.1-34.8%) in 2018. This has been associated with a corresponding drop in the proportion of patients being prescribed warfarin, from 44.8% (95% CI 44.5-45.1%) in 2010 to 33.9% (95% CI 33.6-34.3%) in 2018 (figure 1a). Amongst patients at high risk of stroke, the proportion of patients prescribed anticoagulants rose from 47.2% (95% CI 46.8-47.6%) to 77.2% (95% CI 76.8%-77.6%) between 2008 and 2018 (supplementary figure 1).

A higher proportion of patients with heart failure than without heart failure were prescribed anticoagulation. Among patients with heart failure, 56.8% (95% CI 56-57.8%) were prescribed anticoagulants in 2008, compared to 81.9% (95% CI 81.1-82.7%) in 2018 (supplementary figure 2a). In contrast, 42.8% (95% CI 42.3-43.2%) of patients without heart failure were prescribed anticoagulants in 2008 rising to 68.8% (95% CI 68.3-69.2%) in 2018 (supplementary figure 2b).

Prescription of rate control drugs

There has been a small increase in the proportion of patients prescribed rate control drugs from 69.3% (95% CI 68.9-69.6%) in 2008 to 71.6% (95% CI 71.2%-71.9%) in 2018. Proportions of prescription for diltiazem and verapamil, have remained stable for the study time period. However, prescriptions for beta blockers have increased steadily from 39.5% (95% CI 39.1-39.9%) to 60.7% (95% CI 60.3-61.1%) between 2008 and 2018. This has been associated with a corresponding drop in the proportion of patients prescribed digoxin from 35.6% (95% CI 35.3-36.0%) in 2008 to 16.3% (95% CI 15.9-16.6%) in 2018 (figure 1b).

There was a slight increase in the proportion of high-risk patients (according to CHA_2DS_2-VASc) prescribed rate control drugs between 2008 (72.0% (95% CI 71.7-72.4%) and 2018 (74.3% (95% CI 73.9-74.7 %) in 2018)) (supplementary figure 3).

A higher proportion of patients with heart failure (79.3% (95% CI 78.6-80.0%) in 2008 increasing to 85.5% (95% CI 84.8-86.1%) in 2018)) (supplementary figure 4a) were prescribed rate control drug therapy than those without heart failure (67.0% (95% CI 66.6-617.4%) in 2008 increasing to 68.6% (95% CI 68.2-60.0%) in 2018)) (supplementary figure 4b).

Prescription of rhythm control drugs

The proportion of patients prescribed rhythm control therapy has decreased from 9.5% (95% CI 9.3-9.7%) to 5.4% (95% CI 5.2%-5.6%) between 2008 and 2018. This has corresponded with a drop in the proportion of patients prescribed amiodarone (6.1% (95% CI 5.9-6.3%) in 2008 to 2.3% (95% CI 2.2-2.4%) in 2018). Proportions of prescriptions for dronedarone and propafenone have remained stable and below 1%. The proportion of patients being prescribed flecainide has also remained stable, with a non-significant decrease from 3.1% (95% CI 2.9-3.2%) in 2008 to 2.9% (95% CI 2.7-3.0%) in 2018 (figure 1c).

Rates of prescription of rhythm control drugs were lower in patients at high risk of stroke. These dropped from 8.6% (95% CI 8.4-8.8%) in 2008 to 4.6% (95% CI 4.4-4.8%) in 2018 (supplementary

figure 5). Rates of prescription for rhythm control drugs were similar in patients without heart failure (decreasing from 9.6% (95% CI 9.3-9.8%) in 2008 to 5.5% (95% CI 5.3- 5.7%) in 2018) (supplementary figure 6a) to rates in patients with heart failure (decreasing from 9.2% (95% CI 8.7-9.7%) in 2008 to 5.0% (95% CI 4.6-5.4%) in 2018) (supplementary figure 6b).

DISCUSSION

Since 2008, prescription of pharmacological treatment for the management of AF appears to have become more consistent with the guidance for primary care.

There has been an improvement in the proportion of patients at high risk of stroke prescribed anticoagulation in the last decade. This is consistent with the findings of a previous study of the IMRD database, which examined the trend in prescription of anticoagulants and antiplatelets for AF over time.[2] As discussed in this study, this is likely to be related to the change in UK and European guidance recommending against the use of aspirin as stroke prophylaxis,[5,7] the introduction of NOACs, the prescription of anticoagulation being incentivised through the Quality and Outcomes framework (QOF) and the use of CHA_2DS_2-VASc scoring.[2] This analysis expands on the previous study by exploring trends in use of individual anticoagulants, as well as rate and rhythm control therapies. The findings of this study are also consistent with the results of the Sentinel Stroke National Audit Programme (SSNAP) which has found an increase in the proportion of stroke patients with known AF on anticoagulants at presentation to hospital from 38% to almost 60% from 2013 to 2018.[21]

There has been a decrease in the proportion of patients prescribed warfarin since 2014, with an associated increase in proportion prescribed NOACs. This change in the type of anticoagulants prescribed corresponds with the publication of NICE technology assessments in 2012/3,[22] and updates to clinical guidance.[23] A similar pattern was seen in a study of the UK-based GARFIELD-AF registry[24] (prescribing rates were higher in the GARFIELD cohort, but this study took place in newly diagnosed patients with at least one risk factor for stroke, and also included antiplatelets). This may be due to the advantages NOACs have over warfarin, a fixed dosage and no requirement for international normalised ratio (INR) monitoring.[7]

Beta blockers appeared to be increasingly favoured over digoxin for rate control therapy in the study period. NICE has recommended beta blockers as first line monotherapy since before the start of this study period, but it appears that there may have been slow uptake of this guidance into practice. Concerns that digoxin may cause an increase in mortality may also have contributed to this trend,[25] although there is now evidence to dispute the impact of digoxin on mortality.[,26]

The decrease in the prescription rates for rhythm control therapy, driven by a decrease in prescription of amiodarone, was also described in another UK study.[27] The authors suggested that this was related to evidence that rhythm control offered no benefit over rate control on mortality, with some studies even reporting an increase in mortality.[28,29] The updates to the NICE guidance in 2014, which recommended that rhythm control should be considered as second line after rate control, may also have contributed to the decrease in prescriptions[5] as well as the availability of AF ablation which reduces the need for long-term pharmacological therapy. In the meantime, the EAST

trial has shown superiority of rhythm therapy started in patients within the first year of AF diagnosis.[30] This is likely to lead to a further update of guidelines.

Strengths and limitations

This study used data from a large database that is generalisable to the UK. The data are routinely collected and used by general practitioners to make clinical decisions. Diagnoses were defined by the presence of clinical codes within the database. Many of these diagnoses form part of the QOF assessment and are, therefore, likely to be well recorded. It is likely that conditions not included in the QOF assessment, such as thromboembolism, would still be well recorded due to their clinical significance. Patients with an 'AF resolved' code were excluded to avoid including patients no longer requiring treatment.

A limitation of the study is that the analysis would not capture any medications prescribed in secondary care. NICE CKS[14] recommends referral to secondary care for consideration of rhythm control therapy meaning that those initiated on rhythm control therapy in secondary care just prior to the census date may have been missed. However, those maintained on rhythm control therapy are likely to receive their repeat prescription in primary care and, therefore, would have been captured. "Pill in the pocket" prescriptions of rhythm control therapy (usually flecainide), may also not have been captured within the 90 days prior to the census date, even if prescribed in primary care. However, as the majority of the drugs included in this analysis are likely to have been prescribed in primary care on a long term basis, all repeat prescriptions are likely to have been captured.

The study was not able to capture when treatments were initiated. Given many of the patients prescribed warfarin are likely to have been taking it for a number of years, a more dramatic change in anticoagulant prescription patterns may have been observed if only newly initiated treatment was included. As this was a serial cross-sectional analysis at specific time points, this does not reflect persistence on treatment, and one cannot assume adherence to medication prescribed. It also cannot be assumed that all drugs were prescribed for the management of AF. For instance, anticoagulants may have been prescribed for a previous thromboembolism. Heart failure may be the indication for drugs such as beta blockers. For this reason, a subgroup analysis in patients without heart failure was undertaken.

Finally, due to the exclusion of patients with eGFR ≤30mL/min, the results can only be generalised to patients without severe renal impairment.

Conclusion

Appropriate prescription of anticoagulants for AF has improved over the past decade, with NOACs becoming increasingly favoured over warfarin. Rates of prescribing of rate control in AF remained constant between 2008 and 2018. There has been an increased use of beta blockers, reflecting increased compliance with guidance. Rhythm control drugs are prescribed less frequently than a decade ago in primary care, perhaps reflecting concerns around their safety and effectiveness and delegation of rhythm control therapy prescription to specialist care, as well as potentially shorter duration rhythm therapy if AF is treated by ablation.

ETHICS

Use of IQVIA Medical Research Data (IMRD-UK) is approved by the UK Research Ethics Committee (reference number: 18/LO/0441); in accordance with this approval, the study protocol was reviewed and approved by an independent Scientific Review Committee (SRC) (reference number: 17THIN062). IMRD-UK incorporates data from The Health Improvement Network (THIN), A Cegedim Database. Reference made to THIN is intended to be descriptive of the data asset licensed by IQVIA. This work used de-identified data provided by patients as a part of their routine primary care.

CONFLICT OF INTEREST STATEMENT

LF has received institutional research grants and non-financial support from European Union, British Heart Foundation, Medical Research Council (UK), several biomedical companies and previously DFG. The Institute of Cardiovascular Research, University of Birmingham, has received an Accelerator Award by the British Heart Foundation AA/18/2/34218.

LF is listed as inventor of two patents held by University of Birmingham (Atrial Fibrillation Therapy WO 2015140571, Markers for Atrial Fibrillation WO 2016012783).

CONTRIBUTION STATEMENT

KN, TM, NJA and LF conceived the research question. AS and NJA designed the analysis. AS and KP performed the analysis. KP, AS and NJA drafted the manuscript. PB reviewed the Read codes used in the analysis during the revision process. All authors reviewed the manuscript and provided critical feedback.

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REFERENCES

[1] Public Health England, Atrial fibrillation prevalence estimates for local populations. London: Public Health England, 2019

[2] Adderley NJ, Ryan R, Nirantharakumar K et al. Prevalence and treatment of atrial fibrillation in UK general practice from 2000 to 2016. *Heart* 2019 Jan;105(1):27-33

[3] Williams BA, Chamberlain AM, Blankenship JC et al. Trends in Atrial Fibrillation Incidence Rates Within an Integrated Health Care Delivery System, 2006 to 2018. *JAMA Network Open* 2020;3(8):e2014874-e.[4] Odutayo A, Wong C X, Hsiao A J, et al. Atrial fibrillation and risks of cardiovascular disease, renal disease, and death: systematic review and meta-analysis. *Br Med J* 2016; 354 :i4482 doi:10.1136/bmj.i4482

[5] National Institute for Health and Care Excellence. Atrial fibrillation: the management of atrial fibrillation. NICE clinical guideline 180. London: National Institute for Health and Care Excellence, 2014.

[6] Lip GYH. The ABC pathway: an integrated approach to improve AF management. *Nat Rev Cardio* 2017;14(11):627-8.

[7] Hindricks G, Potpara T, Dagres N et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J*. 2021 Feb 1;42(5):373-498

[8] Velleca M, Costa G, Goldstein L et al. A review of the burden of atrial fibrillation: understanding the impact of the new millennium epidemic across Europe. *EMJ Cardiol* 2019;7[1]:110-118.

[9] Sposato LA , Cipriano LE , Saposnik G , et al . Diagnosis of atrial fibrillation after stroke and transient ischaemic attack: a systematic review and meta-analysis. *Lancet Neurol* 2015;14:377–87.doi:10.1016/S1474-4422(15)70027-X

[10] Jørgensen HS, Nakayama H, Reith J et al. Acute stroke with atrial fibrillation. The Copenhagen Stroke Study. *Stroke* 1996;27(10):1765-9.

[11] Steffel J, Verhamme P, Potpara TS, et al. The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. *Eur Heart J* 2018;39(16):1330-93.

[12] Loo SY, Dell'Aniello S, Huiart L et al. Trends in the prescription of novel oral anticoagulants in UK primary care. *Br J Clin Pharmacol* (2017) 83 2096–2106

[13] National Institute for Health and Care Excellence. Atrial fibrillation: management. In development [GID-NG10100]. London: National Institute for Health and Care Excellence, 2020

[14] National Institute for Health and Care Excellence. NICE Clinical Knowledge Summaries. Atrial Fibrillation. Scenario: management of AF. London: National Institute of Health and Care Excellence, 2019

[15] Blak BT, Thompson M, Dattani H et al. Generalisability of The Health Improvement Network (THIN) database: demographics, chronic disease prevalence and mortality rates. *Inform Prim Care* 2011;19(4):251-5.

[16] Booth N. What are the Read codes? *Health Libr Rev* 1994, 11, 177-182

[17] Maguire A, Blak BT, Thompson M. The importance of defining periods of complete mortality reporting for research using automated data from primary care. *Pharmacoepidemiol Drug Saf* 2009 Jan;18(1):76-83.

[18] Gokhale, K.M., Chandan, J.S., Toulis, K., Gkoutos, G., Tino, P., Nirantharakumar, K., 2020. Data extraction for epidemiological research (DExtER): a novel tool for automated clinical epidemiology studies. *Eur J of Epidemiol* doi:10.1007/s10654-020-00677-6

[19] NHS Digital. Quality and Outcomes Framework (QOF) business rules v42 2019-2020 baseline release. London: NHS Digital, 2019.

[20]Lip GYH, Nieuwlaat R, Pisters T et al. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. *Chest* 2010 Feb;137(2):263-72.

[21] Sentinel Stroke National Audit Programme (SSNAP). SSSNAP Annual Public Report 2018. King's College London, 2019. Available at: https://www.strokeaudit.org/Documents/National/Clinical/Apr2017Mar2018/Apr2017Mar2018-AnnualReport.aspx [Last accessed: 2021 Feb 05].

[22] National Institute for Health and Care Excellence. Anticoagulants, including direct-acting oral anticoagulants (DOACs). Key therapeutic topic 16. . London: National Institute for Health and Care Excellence, 2016

[23] Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al.. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J* [Internet] 2016;37(38):2893–962. Available at: https://dx.doi.org/10.1093/eurheartj/ehw210 [Last accessed 2021 Feb 05]

[24]Apenteng PN, Gao H, Hobbs FDR et al. Temporal trends in antithrombotic treatment of real-world UK patients with newly diagnosed atrial fibrillation: findings from the GARFIELD-AF registry. *BMJ Open* 2018;**8**:e018905. doi:10.1136/ bmjopen-2017-018905

[25] Lopes RD, Rordorf R, De Ferrari GM, et al. Digoxin and mortality in patients with atrial fibrillation. *J Am Coll Cardiol* 2018; 71:1063–1074

[26] Kotecha D, Bunting KV, Gill SK et al. Effect of Digoxin vs Bisoprolol for Heart Rate Control in Atrial Fibrillation on Patient-Reported Quality of Life. *JAMA* 2020;324(24):2497.

[27] Hayward C, Patel HC ,Patel K, et al. The evolving landscape of oral anti-arrhythmic prescriptions for atrial fibrillation in England: 1998 – 2014. *Eur Heart J – Cardiovasc Pharmacother* 2016 2, 90–94

[28] Wyse DG, Waldo AL, DiMarco JP, Domanski MJ, Rosenberg Y, Schron EB, Kellen JC, Greene HL, Mickel MC, Dalquist JE, Corley SD. A comparison of rate control and rhythm control in patients with atrial fibrillation. *N Engl J Med* 2002; 347:1825 – 1833.

[29] Van Gelder IC, Hagens VE, Bosker HA, Kingma JH, Kamp O, Kingma T, Said SA, Darmanata JI, Timmermans AJ, Tijssen JG, Crijns HJ. A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. *N Engl J Med* 2002;347:1834–1840.

[30] Kirchhof P, Camm AJ, Goette A, Brandes A, Eckardt L, Elvan A, et al. Early Rhythm-Control Therapy in Patients with Atrial Fibrillation. *N Engl J Med* 2020;383(14):1305–16.