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 coexisting heart failure.

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

Conclusions There has been an increase in the proportion of patients with AF at risk of stroke as determined by CHA2DS2-VASc score ≥2.

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

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. At least one-fifth of all strokes are related to AF. 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.

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 £22,423–£23,345 and £13,634–£13,720, respectively, in 2008–2009. Anticoagulation can prevent AF-related strokes in up to two-thirds of patients. 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 CHA2DS2-VASc (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke or transient ischemic attack, vascular disease, age 65 to 74 years, sex category) score ≥2. 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 (apixaban, dabigatran, edoxaban and rivaroxaban). NOACs were approved for use in the UK from 2008. Up until 2020, NICE gave warfarin and NOACs equal weighting as options for anticoagulation; however, updated guidelines, expected to be published in 2021, are likely to recommend NOACs as the first-line choice over warfarin. The European Society of Cardiology has also recommended NOACs as first line in 2020.

For most patients with AF being managed in primary care, rate control treatment is recommended as first line. 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 undertreatment of moderate and high risk patients with AF had been noted as well as overtreatment 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 were 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.37 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 or Vision installation date.

The data extraction and cohort selection were facilitated using the data extraction for epidemiological research (DExtER) tool.18 All analyses were conducted using Stata IC V.14.2.

Study design

Cross-sectional analyses were performed on 1 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 \( \leq 30 \) mL/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 AF 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 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.

\(^{16}\)CHA\(_{DS_{2}}\)-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 \( \geq 75 \) years and history of stroke, transient ischaemic attack 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 online supplemental 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. Ninety-five per cent CIs for proportions were calculated using the normal approximation method. In the primary analysis, patients were stratified as low (CHA\(_{DS_{2}}\)-VASc <2) or high stroke risk (CHA\(_{DS_{2}}\)-VASc \( \geq 2 \)). 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 224,506 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. In 2008, 55.1% of the cohort were male, 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\(_{DS_{2}}\)-VASc changed little between 2008 and 2018.

Prescription of anticoagulants

Between 2008 and 2018, the proportion of patients with AF prescribed anticoagulants increased from 45.3% (95% CI 45.0% to 45.7%) to 71.1% (95% CI 70.7% to 71.5%). NOACs were first prescribed in the study population in 2010, for 2 out of 85,526 patients. This proportion has risen steadily to 34.4% (95% CI 34.1% to 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% to 45.1%) in
2010 to 33.9% (95% CI 33.6% to 34.3%) in 2018 (figure 1A).

Among patients at high risk of stroke, the proportion of patients prescribed anticoagulants rose from 47.2% (95% CI 46.8% to 47.6%) to 77.2% (95% CI 76.8% to 77.6%) between 2008 and 2018 (online supplemental figure 1).

A higher proportion of patients with heart failure are prescribed anticoagulants. Among patients with heart failure, 56.8% (95% CI 56.0% to 57.8%) were prescribed anticoagulants in 2008, compared with 81.9% (95% CI 81.1% to 82.7%) in 2018 (online supplemental figure 2A). In contrast, 42.8% (95% CI 42.3% to 43.2%) of patients without heart failure were prescribed anticoagulants in 2008 rising to 68.8% (95% CI 68.3% to 69.2%) in 2018 (online supplemental 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% to 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% to 39.9%) to 60.7% (95% CI 60.3% to 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% to 36.0%) in 2008 to 16.3% (95% CI 15.9% to 16.6%) in 2018 (figure 1B). There was a slight increase in the proportion of high-risk patients (according to CHA2DS2-VASc) prescribed rate control drugs between 2008 (72.0% (95% CI 71.7% to 72.4%) and 2018 (74.3% (95% CI 73.9% to 74.7%) in 2018)) (online supplemental figure 3).

A higher proportion of patients with heart failure (79.3% (95% CI 78.6% to 80.0%) in 2008 increasing to 85.5% (95% CI 84.8% to 86.1% in 2018)) (online supplemental figure 4A) were prescribed rate control drug therapy than those without heart failure (67.0% (95% CI 66.6% to 67.4%) in 2008 increasing to 68.6% (95% CI 68.2% to 60.0%) in 2018)) (online supplemental figure 4B).

### Prescription of rhythm control drugs

The proportion of patients prescribed rhythm control therapy has decreased from 9.5% (95% CI 9.3% to 9.7%) to 5.4% (95% CI 5.2% to 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% to 6.3%) in 2008 to 2.3% (95% CI 2.2% to 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

### Table 1 Demographic characteristics of patients with atrial fibrillation 2008–2018

| Year       | Population (n) | Male sex, n (%) | Proportions of prescription for rate control drugs | Proportions of prescription for rhythm control drugs |
|------------|----------------|-----------------|--------------------------------------------------|---------------------------------------------------|
|            |                |                 | from 69.3% (95% CI 68.9% to 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% to 39.9%) to 60.7% (95% CI 60.3% to 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% to 36.0%) in 2008 to 16.3% (95% CI 15.9% to 16.6%) in 2018 (figure 1B). There was a slight increase in the proportion of high-risk patients (according to CHA2DS2-VASc) prescribed rate control drugs between 2008 (72.0% (95% CI 71.7% to 72.4%) and 2018 (74.3% (95% CI 73.9% to 74.7%) in 2018)) (online supplemental figure 3).

A higher proportion of patients with heart failure (79.3% (95% CI 78.6% to 80.0%) in 2008 increasing to 85.5% (95% CI 84.8% to 86.1% in 2018)) (online supplemental figure 4A) were prescribed rate control drug therapy than those without heart failure (67.0% (95% CI 66.6% to 67.4%) in 2008 increasing to 68.6% (95% CI 68.2% to 60.0%) in 2018)) (online supplemental figure 4B).
Arrhythmias and sudden death

Figure 1  (A) Percentage of patients in the study population prescribed anticoagulants 2008–2018. (B) Percentage of patients in the study population prescribed rate control drugs 2008–2018. (C) Percentage of patients in the study population prescribed rhythm control drugs 2008–2018. NOAC, non-vitamin K antagonist oral anticoagulant.

3.1% (95% CI 2.9% to 3.2%) in 2008 to 2.9% (95% CI 2.7% to 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% to 8.8%) in 2008 to 4.6% (95% CI 4.4% to 4.8%) in 2018 (online supplemental figure 5). Rates of prescription for rhythm control drugs were similar in patients without heart failure (decreasing from 9.6% (95% CI 9.3% to 9.8%) in 2008 to 5.5%
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 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 2012/2013 and updates to clinical guidance. A similar pattern was seen in a study of the UK-based Global Anticoagulant Registry in the Field-Atrial Fibrillation (GARFIELD-AF) registry (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 monitoring.

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 a slow uptake of this guidance into practice. Concerns that digoxin may cause an increase in mortality may also have contributed to this trend, although there is now evidence to dispute the impact of digoxin on mortality.

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. 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. 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 as well as the availability of AF ablation that reduces the need for long-term pharmacological therapy. In the meantime, the Early Treatment of Atrial Fibrillation for Stroke Prevention Trial (EAST) has shown superiority of rhythm therapy started in patients within the first year of AF diagnosis. 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 Clinical Knowledge Summaries 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

Key messages
What is already known on 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 undertreatment of moderate and high-risk patients with AF, as well as overtreatment 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 might 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 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 10 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.
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 ≤30 mL/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.

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