
Carl Hayward†*, Hitesh C. Patel†, Ketna Patel2, Carlo Di Mario1, Alexander R. Lyon1, Syed Y. Ahsan3, and Edward Rowland3

1NIHR Cardiovascular Biomedical Research Unit, Royal Brompton Hospital, Sydney Street, London SW3 6NP, UK; 2University College London, London, UK; and 3Barts Heart Centre, London, UK

Aims
An important decision in the management of patients with atrial fibrillation is whether to adopt a rate or rhythm control strategy. Options for the latter include oral membrane-active anti-arrhythmic drugs (AADs) or catheter ablation. Recent prescription trends may have been affected by the introduction of dronedarone and an increasing number of reports suggesting increased mortality in those taking AADs. We describe the trend in oral AAD prescriptions in England in the period 1998–2014.

Methods and results
We conducted a retrospective study using data from the Prescription Cost Analysis system, which holds information on every prescription dispensed in the community in England. We obtained data from 1998 to October 2014 for all Class Ia, Ic, and III AADs. Amiodarone and sotalol remain the most commonly prescribed AADs in England, though the use of both is decreasing. There has been a linear increase in the uptake of flecainide. Dronedarone prescriptions peaked in 2011, and our most recent data show that amiiodarone prescriptions are 25-fold those of dronedarone.

Conclusion
There is a decline in the use of amiodarone and sotalol consistent with the growing safety concerns with these drugs along with neutral results from landmark trials comparing rate and rhythm control. Dronedarone has failed to make an impact on AAD prescribing. In contrast, flecainide has seen an increase in use during the study period.

Keywords
Anti-arrhythmic drugs • Atrial fibrillation • Rhythm control • Dronedarone

Introduction
Atrial fibrillation (AF) is the most common arrhythmia and affects ∼850 000 individuals in England. Significant pharmacological advances have been made in stroke prevention in AF with the introduction of four novel oral anticoagulants. These drugs have a better efficacy and safety profile than warfarin and are more convenient. Furthermore, there have been developments in device therapy for stroke prevention with left atrial occlusion devices available to those who cannot be anti-coagulated.

Aside from stroke prophylaxis, the other important clinical consideration in the management of AF is the decision to opt for rate or rhythm control. There has been technological growth in rhythm control strategies with the uptake of catheter ablation. However, cost, availability, and long-term efficacy, among other factors, limit its use to only a few thousand patients/year in England. The area in which there have been limited advances is in anti-arrhythmic medical therapy. Dronedarone has been the only new anti-arrhythmic for long-term rhythm control released in the last 10 years. The hope was that dronedarone would offer the efficacy of amiodarone but without the side-effect profile and so transform the landscape of anti-arrhythmic therapy. Dronedarone received approval in 2009 and is recommended by the European Society of Cardiology (ESC) along with flecainide, amiodarone, propafenone, and sotalol. Since its release, however, numerous safety concerns have surrounded dronedarone and this may have influenced its uptake.
There are few observational studies that have reported on the use of AADs in European populations and those available may be subject to selection bias and are unable to describe temporal changes. Our objective was to describe every anti-arrhythmic drug (AAD) prescription in England, so reducing selection bias, and to do this over a 16-year period in order to describe temporal changes which may relate to the timing of key clinical trial publications and ESC guidelines.

**Methods**

We conducted a comprehensive nationwide retrospective study. Data were obtained from the Prescription Cost Analysis (PCA) system, which holds information on every prescription dispensed in the community in England, covering a population of \( \geq 50 \) million people. Prescriptions dispensed in the other countries of the UK (Scotland, Wales, and Northern Ireland) were not included. The PCA system does not include drugs dispensed in hospitals, mental health trusts, or private prescriptions. Data were available from 1998 to 2014. We limited this study to the six recommended membrane-active AADs. The estimated population of England was derived from the Office for National Statistics, which provides these estimates from 2001 to 2013. The annual prevalence of AF in England was taken from the Health and Social Care Information Centre, which collects data from the Quality and Outcomes Framework, an annual reward and incentive programme for primary care.

Data are presented as counts with no formal inferential statistical testing. The data in the PCA are freely available in the public domain and no patient-identifiable data are available. As such, ethical approval was not sought for this study.

**Results**

The main findings are illustrated in Figure 1. The total number of AADs dispensed increased linearly from 1998 to 2002. Prescriptions increased more slowly after this, peaking in 2004 followed by a steady decline. The majority of AAD prescriptions are for amiodarone or sotalol which, when combined, make up between 74 and 85% of all ADD prescriptions during the time span of the data. Amiodarone and sotalol prescriptions peaked in 2002 and 2008, respectively, following which there has been a steady decline in both. Amiodarone prescriptions initially increased from 769 800/year in 1998 to 1 017 700/year in 2002 and then fell to 635 600/year in 2014. Between 1998 and 2014, sotalol prescriptions increased from 492 400/year to 652 200/year and flecainide prescriptions increased from 151 600/year to 383 600/year. Dronedarone prescriptions changed very little following licensing and remain at \( \sim 25 \) 000/year.
Disopyramide and propafenone are not commonly used; disopyramide prescriptions have more than halved over the 16-year period, whereas propafenone use remained at low levels. Dronedarone prescriptions increased in the first 2 years that the drug was available, reaching levels similar to propafenone and disopyramide but its use then plateaued. Amiodarone prescriptions were 25-fold greater than prescriptions of dronedarone in 2014.

Data on the prevalence of AF in primary care for England were available from 2006 to 2013. This demonstrates an increase in the prevalence of AF from 692,054 in 2006 to 883,938 in 2013 (Figure 2).

Discussion

The main findings of this study are that: (i) the use of AADs have fallen over the last decade; (ii) dronedarone has had very little clinical uptake in England; (iii) current trends in prescription show that amiodarone and sotalol are prescribed most commonly but on the decline while flecainide use is increasing.

Our data in the context of published observational studies

There are few observational studies that have reported on the use of AADs in European populations. The PREFER in the AF registry enrolled 7243 patients from seven European countries. The three most commonly prescribed AADs in these patients across the seven countries were amiodarone (51% of all AADs prescribed), flecainide (22%), and sotalol (12%). This registry included 1194 patients from the UK in whom the same three AADs were the most commonly used, but sotalol was used more than flecainide: amiodarone (45% of all AADs prescribed), sotalol (27%), and flecainide (19%). A second observational study recruited 1318 patients and found that the same three AADs were most commonly prescribed: amiodarone (51% of all AADs prescribed), flecainide (36%), and sotalol (2%). Both studies are subject to potential selection bias by including only patients who attended a hospital or office outpatient appointment. Furthermore, both studies looked at recent time periods (2012–14) and in neither were temporal changes examined.

Our data include every prescription in England from 1998 to 2014 and as such allows a true real-world assessment of AAD use and also allows the description of trends during a period that included the publication of key clinical trials and ESC guidelines.

If we compare the UK patients in the PREFER in AF registry with our data for the same time, period differences are apparent. Our data suggest at this time that sotalol was the most commonly prescribed AAD not amiodarone: sotalol (39% of all AADs prescribed), amiodarone (37%), and flecainide (20%).

The PREFER in the AF registry only captured data from 2012 and a valuable aspect of our data is the opportunity to report over a 16-year period which demonstrates that there was an increase in AAD prescriptions from 1998 to 2004, but following this AAD prescriptions have declined (this may be related to the publication of key clinical trials in 2002 demonstrating equivalency of rate and rhythm control strategies). There has also been a change in the order of AADs most commonly prescribed, such that sotalol is now the most commonly prescribed AAD with amiodarone second and flecainide prescriptions are increasing.

Rate vs. rhythm control

Despite a year-on-year increase in the number of people diagnosed with AF in England (Figure 2), there has been a decline in prescriptions of AADs since 2002, in particular amiodarone and sotalol. This change in prescribing behaviour coincided with the publication of the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) and Rate Control vs. Electrical Cardioversion (RACE) trials. Both trials compared rhythm control strategies against rate control and found no significant difference between the two with respect to mortality and composite endpoints. This led to a commonly held belief that persisting with a rhythm control strategy did not benefit patients.

The true message of AFFIRM and other similar trials has been debated. An important finding of both trials is that current AADs are not effective in maintaining sinus rhythm. Only 73.3% of the rhythm control arm of AFFIRM were in sinus rhythm at 3 years. Post hoc analysis suggested that those patients who did maintain sinus rhythm during the trial displayed improved survival (hypothesis-generating only). Furthermore, both AFFIRM and RACE allowed discontinuation of anti-coagulation in the rhythm control arm 4 weeks after achieving sinus rhythm, which may have increased stroke rates and does not reflect current best practice.

Ionescu-Ittu et al. performed a retrospective cohort study of patients admitted with AF and compared mortality between those who received a rate vs. rhythm control approach. Attempts were made to control for baseline differences between the two groups of patients using propensity scores and adjustment for co-variates on a Cox proportional hazards model. Data were analysed for 26,130 patients with a mean follow-up of 3.1 years. There was no difference in survival between the two groups at 4 years, but there was a risk reduction noted at 5- and 8-year follow-up for those receiving a rhythm control strategy. Randomized control trials are superior to observational studies and we eagerly await the results from the Catheter Ablation vs. Anti-arrhythmic Drug Therapy for Atrial Fibrillation (CABANA) and Early Treatment of Atrial Fibrillation for Stroke Prevention (EAST) trials to move the rate vs. rhythm control debate forward.

The European Heart Rhythm Association survey suggested that cardiologists have not been dissuaded by the AFFIRM trial and are
willing to attempt rhythm control in their patients. In centres representing 17 countries across Europe, ~60% of patients were offered a rhythm control strategy after the first detected episode of AF as were up to 50% of young patients even if they tolerated the arrhythmia well. The main limitation is clearly not a lack of desire to achieve rhythm control, rather a lack of widely available and effective tools.

The impact of dronedarone

It was hoped that dronedarone would be a new tool in the cardiologist's armamentarium to achieve rhythm control with the efficacy of amiodarone but without the toxicity. The European Trial in Atrial Fibrillation or Flutter Patients receiving Dronedarone for the Maintenance of Sinus Rhythm (EURIDIS) and American-Australian-African Trial with Dronedarone in Atrial Fibrillation or Flutter Patients for the Maintenance of Sinus Rhythm (ADONIS) trials demonstrated that dronedarone was significantly better than placebo at maintaining sinus rhythm. The ATHENA trial showed that, when compared with placebo, dronedarone reduced the incidence of cardiovascular death and hospitalization. However, the Randomized, Double Blind Trial to Evaluate the Efficacy and Safety of Dronedarone vs. Amiodarone for at Least 6 Months for the Maintenance of Sinus Rhythm in Patients with AF (DIONYSOS) compared dronedarone with amiodarone and found it to be less effective in preventing AF recurrence. There were fewer deaths reported in the dronedarone group than in the amiodarone group in the DIONYSOS trial, but there was no conclusive evidence for improved mortality.

More concerning than the lack of efficacy of dronedarone are the safety concerns raised. The Antiarrhythmic Trial with Dronedarone in Moderate to Severe CHF Evaluating Morbidity Decrease (AN-DROMEDA) randomized 627 patients with a reduced ejection fraction, a recent heart failure admission, and New York Heart Association class III or IV symptoms (AF was not a prerequisite) to dronedarone or placebo. The primary outcome was death from any cause or heart failure hospitalization. The safety monitoring board recommended that the trial stop after only 7 months due to a significant increase in mortality in those patients taking the active medication. There were 10 deaths in the dronedarone arm and 2 in the placebo group; the small numbers may have led to a false result. In searching for a plausible mechanistic explanation, other than negative inotropic effects of the drug, the authors uncovered that there was a higher rate of angiotensin-converting enzyme inhibitor withdrawal in the active arm as dronedarone elevates serum creatinine.

Finally, the Permanent Atrial Fibrillation Outcome Study Using Dronedarone on Top of Standard Therapy (PALLAS) sought to investigate the role of dronedarone upon cardiovascular events or death in patients with permanent AF and significant cardiac risk factors. The study was stopped after 12 months at the recommendation of the data safety committee, by which stage 3236 patients had undergone randomization. The dronedarone cohort had more than double the risk (hazard ratio 2.29) of experiencing the co-primary endpoint compared with placebo. The results of these trials may explain the low uptake of dronedarone in England, despite the drug receiving approval from the National Institute of Health and Care Excellence (NICE). Dronedarone use may be bolstered over the coming years with emerging evidence for the efficacy of low-dose dronedarone in combination with ranolazine in the HARMONY trial (A Study to Evaluate the Effect of Ranolazine and Dronedarone When Given Alone and in Combination in Patients With Paroxysmal Atrial Fibrillation). Phase 3 trials to further assess this combination therapy are being planned.

Current trends

Flecainide remains the only AAD that is increasing in use in England. It has been available for 40 years and there is evidence to suggest that it may be more potent than amiodarone at maintaining sinus rhythm and reducing symptoms in patients with paroxysmal AF. There is evidence that it is safe in selected patients: in a meta-analysis involving 4811 patients, spanning 2015 years of exposure to flecainide only 8 deaths occurred. However, a significant limitation in the use of flecainide remains the risk to those with coronary artery disease or structural heart disease. The Cardiac Arrhythmia Suppression Pressure Trial (CAST) demonstrated that flecainide resulted in more arrhythmia-related deaths and a significant increase in total mortality in patients with a prior myocardial infarction. A more recent, retrospective study also demonstrated that those patients who were prescribed flecainide had an increased risk of sudden cardiac death. The majority of patients in this study did not have coronary or structural heart disease, suggesting potential safety concerns for a wider group of patients. The safety concerns surrounding flecainide, particularly in those with comorbid coronary or structural heart disease, is a major limitation since these co-morbidities are often present in the ageing population with AF. A significant confounder in our data is the absence of information on the indication for which the AADs are prescribed. Many of these AADs can be prescribed for arrhythmias other than AF, such as supraventricular tachycardia or ventricular tachycardia. A component of the changing trends in AAD prescription may be related to the treatment of these non-AF arrhythmias; however, it is likely that atrial arrhythmias are the predominant indication.

Limitations

Our data only represent prescriptions in England, which may not be representative for the rest of Europe. We limited our study to membrane-active AADs and did not include beta-blockers, primarily as this drug is commonly used for indications other than rhythm control (e.g., rate control, heart failure, and hypertension), which we would not be able to distinguish between. It is likely that beta-blockers are extensively used for rhythm control and, indeed, the most recent NICE guidance (2014) recommended standard beta-blockers (not sotalol) as first-line treatment unless there are contraindications. Beta-blockers are only modestly effective in maintaining sinus rhythm and some of their perceived benefits may be explained by improved rate control as opposed to rhythm control. Their popularity and endorsement as a first-line agent is driven by safety rather than efficacy, a key guiding principle of the ESC pertaining to AAD therapy in AF.

The data presented are the number of prescriptions dispensed in a year rather than the number of patients on AADs; this does not detract from the main findings of this study as we sought to identify trends in prescribing behaviour rather than the prevalence of patients on AADs. Prescriptions in England tend to be for 1–3 months...
supply, which may aid an understanding of the broad number of patients on AADs. Amiodarone and sotalol may also be used for the treatment of ventricular arrhythmias and our data are unable to distinguish by indication. However, ventricular arrhythmias are significantly rarer than AF. No data were available on patient demographics which means we cannot determine if changes with time or differential use of AADs are due to patients factors such as age or gender.

The strength of the study is its longitudinal span of 16 years that comprehensively captures all prescriptions dispensed in England, where there is universal access to healthcare including treatments.

**Conclusion**

We have demonstrated that the use of AADs in England is declining despite the increasing burden of AF. Clinicians are prescribing less amiodarone and sotalol and instead are showing greater confidence in flecainide. Dronedarone has not made a significant impact on the AAD landscape in England.

**Funding**

C.H. and H.C.P. are funded by the National Institute of Health Research, Biomedical Research Unit, Royal Brompton Hospital, London, UK.

**Conflict of interest: none declared.**

**References**


