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## Rhythm control agents and adverse events in patients with atrial fibrillation

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**Rhythm control agents and adverse events in patients with atrial fibrillation**

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**Title:**

Adverse events and predictors of treatment discontinuation of rhythm control agents in patients with atrial fibrillation

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2  
3 **Adverse events and predictors of treatment discontinuation of rhythm control**  
4 **agents in patients with atrial fibrillation**  
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10 **Taylor CJ, Hodgkinson J, Hobbs FDR**  
11

12  
13  
14  
15 **Abstract**

16  
17 **Background**

18  
19 Atrial fibrillation (AF) is the commonest rhythm disorder and has major impact on  
20 patients. Controversy remains around the best treatment strategy between rate and  
21 rhythm control (in addition to adequate thromboprophylaxis). Rhythm control agents  
22 are associated with clinically important adverse events.  
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31  
32 **Aim**

33  
34 To assess the risk of adverse events in patients with AF receiving rhythm control  
35 agents and identify predictors of treatment discontinuation.  
36  
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40

41 **Design of study**

42  
43 Retrospective case control note review and outcome linkage analysis.  
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47

48 **Setting**

49  
50 Patients with a diagnosis of AF receiving amiodarone, flecainide or sotalol in  
51 practices registered with the General Practice Research Database (GPRD) in the UK.  
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## Method

Retrospective case control note review and outcome linkage analysis on the GPRD routine clinical dataset to evaluate the adverse events and predictors of treatment discontinuation in patients using licensed rhythm modifying medication.

## Results

Adverse events are more common in patients currently or previously taking amiodarone, flecainide or sotalol than age and gender matched controls. All three antiarrhythmics were associated with increased all-cause mortality. Congestive heart failure was more common in all amiodarone and sotalol users as well as past users of flecainide. Thyroid disease was more common in patients treated with amiodarone and sotalol but only amiodarone had an increased risk of pulmonary toxicity. The number of patients with liver failure was too small in all cases for statistical analysis.

## Conclusion

The rhythm control agents amiodarone, flecainide and sotalol have significant adverse effects which can lead to discontinuation of their use. This should be considered when deciding the most appropriate treatment option for patients with AF.

## Keywords

Atrial fibrillation, antiarrhythmics, amiodarone, flecainide, sotalol, adverse effects

## What is already known about this topic?

Atrial fibrillation (AF) is an increasingly common problem globally. There is debate about whether rate or rhythm control is the most appropriate treatment strategy.

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2  
3 Rhythm control agents are commonly used in the treatment of patients with AF but  
4  
5 may be associated with side effects.  
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9

### 10 **What does this article add?**

11  
12 Patients with atrial fibrillation treated with amiodarone, flecainide or sotalol are at  
13  
14 increased risk of clinically significant adverse events which can lead to  
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16 discontinuation of their use.  
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### 25 **Introduction**

26  
27 Atrial fibrillation (AF) is the commonest rhythm disorder. The prevalence increases  
28  
29 with age from less than 1 in 1000 in under 35s to over 100 in 1000 in people age 85  
30  
31 and over<sup>1</sup>. AF is an independent risk factor for thromboembolic stroke<sup>2</sup> and heart  
32  
33 failure<sup>3</sup> and is associated with increased morbidity and mortality<sup>4</sup>. The risk of  
34  
35 thromboembolism can be reduced by anti-platelet<sup>5</sup> or anticoagulation<sup>6</sup> therapy.  
36  
37  
38 Uncertainty remains around whether control of ventricular rate or conversion to sinus  
39  
40 rhythm is the most appropriate treatment strategy for AF. In the Atrial Fibrillation  
41  
42 Follow-up Investigation of Rhythm Management (AFFIRM) study, a large  
43  
44 randomised controlled trial involving over 4000 patients with AF and other risk  
45  
46 factors for stroke or death, mortality rates were similar in those treated with rate or  
47  
48 rhythm control therapy and side effects were higher in the rhythm-control group<sup>7</sup>.  
49  
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55 NICE guidelines on the management of AF published in 2006 suggests rhythm  
56  
57 control is preferable to rate control in the following patient groups with persistent  
58  
59 AF<sup>27</sup>:  
60

- Symptomatic
- Younger
- Presenting for the first time with lone AF
- Secondary to a treated or corrected precipitant
- With congestive heart failure

The commonest agents used for rhythm control are amiodarone, flecainide and sotalol.

Amiodarone is a class III antiarrhythmic drug<sup>8</sup> which acts by blocking sodium, potassium and calcium channels on cardiac myocytes to increase the refractory period of the cardiac action potential which can result in a longer QT interval being seen on electrocardiogram. It also has some class II activity by non-competitive B blockade<sup>9</sup>.

Amiodarone may also prevent electrical remodelling which can result from atrial overactivity<sup>10</sup>. Amiodarone has a number of significant adverse effects which can limit its use including pro-arrhythmic effects, thyroid disease, hepatotoxicity, pulmonary toxicity and ophthalmological disorders.

Flecainide is a class 1c anti-arrhythmic<sup>8</sup>. It acts by blocking sodium channels to reduce intracardiac conduction<sup>11</sup>. It has been associated with fatal arrhythmias in patients with structural heart disease.

Sotalol is a non-selective  $\beta$  blocker which also has class III anti-arrhythmic action<sup>8</sup>. It leads to an increase in duration of the cardiac action potential and slows repolarisation

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2  
3 giving rise to a prolongation of the QT interval on ECG which may predispose to  
4  
5 ventricular arrhythmias<sup>12</sup>.  
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10 In this article we present a study using data from the General Practice Research  
11  
12 Database (GPRD) evaluating the adverse events and predictors of treatment  
13  
14 discontinuation in patients using these commonly prescribed anti-arrhythmic agents.  
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19

## 20 **Methods**

21  
22 We conducted a retrospective case control note review and outcome linkage analysis  
23  
24 on the GPRD routine clinical dataset to evaluate the adverse events and predictors of  
25  
26 treatment discontinuation in patients using licensed rhythm modifying medication  
27  
28 (amiodarone, flecainide and sotalol).  
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## 34 **Population for Analysis**

35  
36 The GPRD collects data from over 350 practices in the UK. More than three million  
37  
38 patients are currently contributing data and the system has over 35 million patient  
39  
40 years on record making it the largest primary care routine patient record database in  
41  
42 the world. Information including patients demographics, diagnoses, prescribing  
43  
44 history and test results are collected using VISION software and collated centrally.  
45  
46 The GPRD has been widely used for pharmacoepidemiological research and data is  
47  
48 quality assured by checks for consistency and completeness of data recording and  
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50 adherence to GPRD guidelines<sup>13</sup>.  
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### Cases in this Linkage Study

Participants were 18 years and older with a diagnosis of atrial fibrillation. Patients were included in the study if they had a first prescription of rhythm modifying medication, namely amiodarone, flecainide or sotalol, at least 12 months after the start of GPRD data collection and a second prescription of the same drug within six months of the first. Follow-up of these patients began on the date of the second prescription, representing chronic rhythm medication users. Each amiodarone, flecainide and sotalol user was matched to three control patients by age (within 2 years), gender, practice and calendar time. Eligible controls had at least 12 months data prior to the start date. Patients with a record of AF or “non-specific heart rhythm disorders” were excluded as controls.

### Analysis

We evaluated the occurrence of known adverse events associated with amiodarone, flecainide and sotalol in patients on treatment compared with controls. For amiodarone we included hyperthyroidism and hypothyroidism, acute and chronic liver failure, pulmonary toxicity (pneumonitis or interstitial/alveolar pneumonitis), visual impairment (including blurred vision, visual halos, optic neuropathy or optic neuritis), congestive heart failure and all cause mortality. In the flecainide group we included acute and chronic liver disease, congestive heart failure and death. In the sotalol group we included hyperthyroidism and hypothyroidism, acute and chronic liver failure, congestive heart failure and all cause mortality.

The follow-up of all three groups was divided into current and past use. The periods of current use included the time from the date of a prescription for amiodarone,

1  
2  
3 flecainide and sotalol until the expected end of treatment (based on the prescribed  
4 daily dose and number of tablets) plus an offset period. The period of offset was 2  
5  
6 months for amiodarone and 1 month for sotalol or flecainide to take into account their  
7  
8 different half lives. The period of past use was from the expected end of treatment  
9  
10 plus the offset period until the end of the GPRD data collection or patients death,  
11  
12 whichever came first. Patients taking amiodarone, flecainide or sotalol were censored  
13  
14 if they switched treatment to another antiarrhythmic.  
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### 22 Statistical Methods

23  
24 We used Poisson regression to compare current users of amiodarone, flecainide and  
25  
26 sotalol with past users and controls. Potential confounders included in the regression  
27  
28 model were age, gender, body mass index, smoking history, alcohol use, history of  
29  
30 ischaemic heart disease, heart failure, hypertension, cerebrovascular disease, diabetes  
31  
32 mellitus, hyperthyroidism, prior drug use of statins, angiotensin receptor blockers and  
33  
34 oral glucocorticoids, number of GP visits prior in the six to twelve months prior to  
35  
36 index date and the socio-economic class of the practice region.  
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### 43 Data Mining Exercise

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45 We also conducted a data mining sensitivity analysis to explore any differences in  
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47 symptoms between those who stopped and those who continued treatment with  
48  
49 amiodarone, flecainide or sotalol. Each patient who discontinued treatment was  
50  
51 matched by age (within 5 years), gender and duration of treatment (<1 year, 1-3 years  
52  
53 3+ years) to one patient who continued treatment with the same drug. The symptoms  
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55 recorded between the last prescription and time of treatment discontinuation were  
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60 evaluated in patients who stopped treatment. A period of similar length was also

evaluated in those who continued treatment. Conditional logistic regression was used to determine the symptoms most commonly reported by those stopping treatment compared with those who did not.

## **Results**

A summary of the number and characteristics of patients involved in each analysis are shown in table 1.

	Amiodarone	Flecainide	Sotalol
Number of cases	8,229	1,335	5,365
Number of controls	24,652	4,032	16,122
Age	88% over 65	81% under 75	52% under 70
Percentage male	57%	56%	50%
Taken drug less than 1 year	4,617 (56%)	867 (65%)	3,317 (62%)
Taken drug 1-3 years	2,250 (27%)	314 (24%)	1,308 (24%)
Taken drug for more than 3 years	1,362 (16.5%)	154 (11%)	740 (14%)

Table 1 – Patient characteristics by age, sex and drug duration

### **Adverse Outcomes Related to Amiodarone Use**

As shown in table 2, congestive heart failure was more common in past users of amiodarone than controls. Risk was increased further in current users of amiodarone compared with controls. Risk of hyperthyroidism was increased more than 10 fold in past amiodarone users and more than 20 fold for current users. Hypothyroidism was also significantly more common in past users and higher still in current users. There were only a small number of cases of liver failure so further meaningful statistical analysis was not possible. Pulmonary toxicity was more common in past users and current users but this was not statistically significant. Visual impairment was not significantly different between exposed and unexposed groups either for past users of amiodarone nor current users. All-cause mortality was significantly higher in current amiodarone users than controls.

Results were not affected by excluding patients with an index date prior to 1996.

#### Adverse Outcomes Related to Flecainide Use

Congestive heart failure was more common in past users of flecainide compared with controls but not statistically significantly different in current users. All-cause mortality was increased three-fold in current users of flecainide compared with the unexposed group. The number of cases of liver failure was small so statistical evaluation was not possible.

Excluding patients with an index date prior to 1996 did not alter these findings.

#### Adverse Outcomes Related to Sotalol Use

Congestive heart failure was more common in current users than controls and risk increased further for past users. All cause mortality was increased more than two-fold in the sotalol group. Hyperthyroidism was increased in current users and increased further in past users compared with controls. The risk of hypothyroidism was slightly increased in current users and further increased in past users of sotalol. The number of cases of liver failure was too small for analysis. There was no significant difference in pulmonary toxicity between exposed and unexposed groups for both past or current users.

Results were not affected by excluding patients with an index date prior to 1996.

Adverse effect	Amiodarone RR (95% CI)		Flecainide RR (95% CI)		Sotalol RR (95% CI)	
	Past user	Current user	Past user	Current user	Past user	Current user
All-cause mortality	4.48 (4.21-4.76)	-	3.01 (2.42-3.61)	-	2.61 (2.36-2.85)	-

Congestive heart failure	2.50 (2.08-2.91)	3.79 (3.22-4.36)	3.99 (2.18-5.81)	1.76 (0.90-2.62)	1.55 (1.21-1.88)	2.19 (1.71-2.67)
Hyperthyroidism	10.37 (6.63-14.11)	20.73 (13.74-27.72)	-	-	6.23 (3.11-9.35)	4.74 (2.36-7.12)
Hypothyroidism	2.33 (1.89-2.77)	9.00 (7.67-10.33)	-	-	2.35 (1.80-2.91)	1.35 (1.02-1.69)
Liver failure	NA	NA	NA	NA	NA	NA
Pulmonary toxicity	2.01 (0.62-3.40)	2.35 (0.81-3.88)	-	-	2.94 (-0.48-6.35)	1.34 (-0.33-3.01)
Visual impairment	0.94 (0.51-1.38)	1.62 (0.97-2.28)	-	-	-	-

Table 2 – Relative risk of adverse effects of amiodarone, flecainide or sotalol in cases compared with controls

### Data Mining Exercise

Possible causes for discontinuation of amiodarone by READ chapter included adverse effects, atrial fibrillation/flutter, hypertension, left ventricular failure and cardiac dysrhythmias. Reasons for cessation of flecainide included atrial fibrillation/flutter and adverse events. Reasons for sotalol discontinuation included dysrhythmias, atrial fibrillation/flutter, hypertension and adverse effects.

### Conclusions

#### *Summary of main findings*

Adverse events are much more common in patients currently or previously taking antiarrhythmics than age and gender matched controls, especially for amiodarone users. In patients with atrial fibrillation, all three antiarrhythmics were associated with increased all-cause mortality. Congestive heart failure was more common in all amiodarone and sotalol users as well as past users of flecainide. Thyroid disease was more common in patients treated with amiodarone and sotalol but only amiodarone had an increased risk of pulmonary toxicity. The number of patients with liver failure was too small in all cases for statistical analysis.

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3 The adverse events arising in patients treated with amiodarone, flecainide and sotalol  
4  
5 were similar to the reasons given for discontinuation of treatment in the data mining  
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8 exercise.  
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12 Congestive heart failure is a risk factor for AF<sup>11</sup> so this association in all groups was  
13  
14 not surprising. Also, some guidelines suggest rhythm rather than rate-control is the  
15  
16 preferred treatment for congestive heart failure further explaining the increased risk  
17  
18 seen in patients taking rhythm-control agents compared to control<sup>27</sup>. Amiodarone has  
19  
20 a causal link with thyroid disease and pulmonary toxicity however a causal  
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22 association between sotalol and thyroid disease has not previously been well  
23  
24 recognised.  $\beta$  blockers are used to manage patients with hyperthyroidism which may  
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26 explain this association although the reason for an increased incidence of  
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28 hypothyroidism in patients taking sotalol is less clear.  
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### 36 *Strengths and limitations of the study*

37  
38 The GPRD is a large well-validated database containing information on patients from  
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40 wide demographic backgrounds. The system allows complex analyses of adverse  
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42 events recorded in patients with atrial fibrillation and receiving anti-arrhythmic  
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44 medications.  
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51 The criterion for diagnosis of AF was unclear and may have been on clinical grounds,  
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53 by electrocardiogram or by a specialist but this is impossible to elucidate from the  
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55 GPRD system. There may also be a significant time interval between the time data  
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57 was recorded to the time of this study and clinical practice may have changed during  
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3 this period, however, analysis excluding data prior to 1996 did not significantly alter  
4  
5 the results.  
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10 The study compared patients with atrial fibrillation taking antiarrhythmic medications  
11 with controls who both did not have AF and were not taking antiarrhythmic  
12 medications. There is a well recognised excess mortality in all patients with AF<sup>4</sup>  
13 which may explain some of this result, furthermore, patients treated with rhythm  
14 rather than rate control may have worse prognosis disease. However, at least some of  
15 this effect could also be due to malignant side effects of anti-arrhythmic medications.  
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27 The number of patients with liver failure was too small for meaningful analysis  
28 however it may have been interesting to examine the liver function tests in cases and  
29 controls to see if there was a difference between the two groups.  
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36 *Comparison with existing literature*  
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### 41 **Amiodarone**

#### 42 Proarrhythmic effects

43 Prolongation of the QT interval in patients taking amiodarone can predispose to  
44 torsade de pointes (TdP), polymorphic ventricular fibrillation, which can be fatal. The  
45 incidence of TdP in patients prescribed amiodarone is however less than 1%<sup>14</sup>. The  
46 risk of TdP is increased in the presence of electrolyte abnormalities or concurrent pro-  
47 arrhythmogenic medications<sup>15</sup>. The most common arrhythmia associated with  
48 amiodarone use is bradycardia which can be profound in older patients with a history  
49 of ischaemic heart disease and may require pacing<sup>16</sup>.  
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### Thyroid disease

Amiodarone is associated with thyroid disorders which can range from subclinical abnormalities found on thyroid function tests to clinically apparent hypo- and hyperthyroidism<sup>17</sup>. Hypothyroidism is more common in women and patients with antithyroid antibodies<sup>18</sup>, however, in a sub-study of the Sotalol Amiodarone Atrial Fibrillation Efficacy Trial (SAFE-T) involving mostly male patients with an average age of 67 years, subclinical hypothyroidism was seen in 25.8% of patients treated with amiodarone compared with 6.6% of controls ( $p < 0.0001$ ) and clinically significant hypothyroidism was found in 5.0% of amiodarone treated patients compared with 0.3% of controls ( $p < 0.001$ ). There was no statistically significant difference in hyperthyroidism in this subgroup between amiodarone-treated patients and controls<sup>19</sup> however, elsewhere estimates of hyperthyroidism range from 1 to 23% in patients taking amiodarone<sup>20</sup>.

### Hepatotoxicity

Elevated liver enzymes are seen in 15-30% of patients taking amiodarone and annual incidence of hepatitis and cirrhosis is 0.6%<sup>21</sup>. This is more common in patients on high doses of amiodarone but has been reported in those receiving low dose oral therapy<sup>22</sup>.

### Pulmonary toxicity

Amiodarone pulmonary toxicity (APT) is estimated to occur in 5-7% of patients receiving amiodarone. Mortality is approximately 5-10%<sup>23</sup>. It is most common amongst patients undergoing cardiac surgery who are receiving high doses of

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3 amiodarone to prevent ventricular arrhythmia however APT has also been seen in  
4  
5 patients following lower doses of oral treatment<sup>24</sup>.  
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### 10 Ophthalmological Disorders

11  
12 Corneal deposits are seen in up to 100% of patients receiving amiodarone. These  
13  
14 rarely impair vision. Optic neuritis has also been associated with amiodarone therapy  
15  
16 although a causal link is not certain<sup>25</sup>. This occurs in less than 1% of patients and  
17  
18 routine retinal screening has not been shown to be beneficial<sup>26</sup>.  
19  
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24  
25 Amiodarone is recommended in the National Institute of Health and Clinical  
26  
27 Excellence (NICE) guidelines for use in atrial fibrillation only after failure of other  
28  
29 treatments<sup>27</sup> and is most commonly initiated by a specialist. The routine tests  
30  
31 recommended for monitoring of patients are shown in table 3.  
32  
33  
34

Adverse effect	Test	Frequency
Arrhythmia	Electrocardiogram	At baseline Every 12 months
Hypo/hyperthyroidism	Thyroid function tests	At baseline Every 6 months
Hepatotoxicity	Liver function tests	At baseline Every 6 months
Pulmonary toxicity	Chest x-ray	At baseline Every 12 months
Ophthalmological disorders	Ophthalmological examination	At baseline if pre-existing visual impairment If symptoms occur

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49  
50 Table 3 – Routine testing in patients receiving amiodarone<sup>28</sup>

### 51 Flecainide

52  
53 Flecainide was found to increase mortality in patients with a history of myocardial  
54  
55 infarction and asymptomatic or mild ventricular arrhythmias in the Cardiac  
56  
57 Arrhythmia Suppression Trial (CAST) study<sup>29</sup>. As a result of these findings,  
58  
59 flecainide is contraindicated in patients with structural heart disease. The drug does  
60

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2  
3 however have a role as “pill-in-the-pocket” therapy for those with known paroxysmal  
4  
5 AF. In this approach to treatment, patients with at least one episode of previously  
6  
7 documented AF carry a single dose of flecainide with them and take the medication at  
8  
9 the onset of symptoms. A study of 165 patients with a total of 618 AF episodes  
10  
11 presenting with sudden onset of palpitations without haemodynamic compromise  
12  
13 (systolic BP 100 or more and mean heart rate of greater than 70) found that 94% of  
14  
15 episodes were terminated by flecainide within a mean time of 113 minutes. Side  
16  
17 effects were infrequent with one episode of rapid atrial flutter and 11 cases of non-  
18  
19 cardiac side effects including nausea, vertigo and asthenia<sup>30</sup>.  
20  
21  
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27 Flecainide is also indicated for rhythm control in persistent AF in patients with a  
28  
29 structurally normal heart<sup>27</sup>. A systematic review, which included 5 trials involving  
30  
31 flecainide following cardioversion, found a reduction in recurrence rate of AF. There  
32  
33 was however an increase in withdrawal of treatment in the flecainide groups  
34  
35 compared with control due to side effects including proarrhythmic events<sup>31</sup>.  
36  
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41 Flecainide can be fatal in overdose, due to widening of the QRS complex and  
42  
43 prolongation of the PR interval seen on ECG predisposing to ventricular tachycardia  
44  
45 or bradycardic episodes requiring pacing<sup>32 33</sup>.  
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### 50 **Sotalol**

51  
52 In the Sotalol Amiodarone Atrial Fibrillation Efficacy Trial (SAFE-T), amiodarone  
53  
54 and sotalol were found to have equivalent efficacy for conversion to sinus rhythm  
55  
56 (27.1% v 24.2%, p=0.45) but amiodarone was superior in maintaining sinus rhythm  
57  
58 (median time to recurrence of AF 487 days v 74 days, p<0.001) except in patients  
59  
60

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3 with ischaemic heart disease where both drugs were equivalent. Sotalol was more  
4  
5 efficacious than placebo in all groups<sup>34</sup>.  
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9  
10 The main cardiovascular side effect of sotalol relates to prolongation of the QT  
11  
12 interval which can predispose to torsade de pointes<sup>35</sup>. In a systematic review of 9  
13  
14 studies comparing sotalol with control, there was an increased risk of proarrhythmic  
15  
16 events in the sotalol groups (OR 2.20, 95% CI 1.31-3.69)<sup>31</sup>.  
17  
18

19  
20  
21 In a substudy of the AFFIRM trial, adverse events causing discontinuation of  
22  
23 treatment in the 135 patients in the sotalol arm included congestive heart failure  
24  
25 (2.2%), bradycardia (2.2%), gastrointestinal events (4.4%), pulmonary events (0.7%)  
26  
27 and syncope (0.7%)<sup>36</sup>. Another study investigating long term efficacy and safety of  
28  
29 sotalol in 106 patients found 22% had tolerable side effects such as gastrointestinal  
30  
31 discomfort (2%), neurological disturbance (11%), asymptomatic bradycardia (7%)  
32  
33 and general weakness (2%). A further 10% discontinued treatment due to significant  
34  
35 adverse effects, 4% of these were due to proarrhythmic events and the remainder were  
36  
37 due to asymptomatic QT prolongation, congestive heart failure, symptomatic  
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39 bradycardia and gastrointestinal events.  
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48  
49 Adverse events associated with antiarrhythmic agents are commonly described in the  
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51 literature as discussed above, however, they continue to be commonly prescribed. A  
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53 Canadian study looking at drug use in 465 patients with new onset AF found that  
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55 36.4% (92/253) of patients taking sotalol and 64.1% (25/39) of patients taking  
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57 amiodarone had contraindications or warnings. The number of patients taking  
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59 flecainide was small but 33% (2/6) patients also had contraindications or warnings<sup>37</sup>.  
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### *Implications for future research and practice*

Atrial fibrillation is increasingly common as the population ages and survival from ischaemic heart disease improves. AF guidelines recommend rhythm-control agents for younger patients, those who are symptomatic, present for the first time with lone AF or have congestive heart failure<sup>27</sup>. However, the AFFIRM study found no mortality benefit from rhythm control compared to rate control and a higher rate of adverse events in patients taking rhythm control agents. Further research is required to establish the benefit-risk ratio of rhythm-control treatments in the subgroups of patients recommended to receive these agents. Patients with atrial fibrillation should be carefully counselled about potential adverse effects before starting rhythm-control agents both to allow informed consent and ensure symptoms of adverse events are recognised and reported by the patient early to allow discontinuation or change of treatment as required.

### Author contributions

FDRH, JH and CJT discussed the data prior to preparing the manuscript. JH and CJT undertook the literature review. CJT wrote the first draft of the manuscript and FDRH and JM edited the manuscript. All three authors reviewed the final version.

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## Rhythm control agents and adverse events in patients with atrial fibrillation

**Deleted:** Adverse events and predictors of treatment discontinuation of r

Taylor CJ, Hodgkinson J, Hobbs FDR

### Abstract

#### **Background**

Atrial fibrillation (AF) is the commonest rhythm disorder and has major impact on patients. Controversy remains around the best treatment strategy between rate and rhythm control (in addition to adequate thromboprophylaxis). Rhythm control agents are associated with clinically important adverse events.

#### **Aim**

To assess the risk of adverse events in patients with AF receiving rhythm control agents.

**Deleted:** and identify predictors of treatment discontinuation.

#### **Design of study**

Retrospective case control note review and outcome linkage analysis.

#### **Setting**

Patients with a diagnosis of AF receiving amiodarone, flecainide or sotalol in practices registered with the General Practice Research Database (GPRD) in the UK.

## Method

Retrospective case control note review and outcome linkage analysis on the GPRD routine clinical dataset to evaluate the adverse events and predictors of treatment discontinuation in patients using licensed rhythm modifying medication.

## Results

Adverse events are more common in patients currently or previously taking amiodarone, flecainide or sotalol than age and gender matched controls. All three antiarrhythmics were associated with increased all-cause mortality. Congestive heart failure was more common in all amiodarone and sotalol users as well as past users of flecainide. Thyroid disease was more common in patients treated with amiodarone and sotalol but only amiodarone had an increased risk of pulmonary toxicity. The number of patients with liver failure was too small in all cases for statistical analysis.

## Conclusion

The rhythm control agents amiodarone, flecainide and sotalol have significant adverse effects which can lead to discontinuation of their use. This should be considered when deciding the most appropriate treatment option for patients with AF.

## Keywords

Atrial fibrillation, antiarrhythmics, amiodarone, flecainide, sotalol, adverse effects

## Introduction

Atrial fibrillation (AF) is the commonest rhythm disorder. The prevalence increases with age from less than 1 in 1000 in under 35s to over 100 in 1000 in people age 85

1  
2 and over<sup>1</sup>. AF is an independent risk factor for thromboembolic stroke<sup>2</sup> and heart  
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4 failure<sup>3</sup> and is associated with increased morbidity and mortality<sup>4</sup>. The risk of  
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6 thromboembolism can be reduced by anti-platelet<sup>5</sup> or anticoagulation<sup>6</sup> therapy.  
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Uncertainty remains around whether control of ventricular rate or conversion to sinus rhythm is the most appropriate treatment strategy for AF. In the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study, a large randomised controlled trial involving over 4000 patients with AF and other risk factors for stroke or death, mortality rates were similar in those treated with rate or rhythm control therapy and side effects were higher in the rhythm-control group<sup>7</sup>.

NICE guidelines on the management of AF published in 2006 suggests rhythm control is preferable to rate control in the following patient groups with persistent

AF<sup>27</sup>.

- Symptomatic
- Younger
- Presenting for the first time with lone AF
- Secondary to a treated or corrected precipitant
- With congestive heart failure

The commonest agents used for rhythm control are amiodarone, flecainide and sotalol.

Amiodarone is a class III antiarrhythmic drug<sup>8</sup> which acts by blocking sodium, potassium and calcium channels on cardiac myocytes to increase the refractory period of the cardiac action potential which can result in a longer QT interval being seen on

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2 electrocardiogram. It also has some class II activity by non-competitive B blockade<sup>9</sup>.  
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4 Amiodarone may also prevent electrical remodelling which can result from atrial  
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6 overactivity<sup>10</sup>. Amiodarone has a number of significant adverse effects which can  
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8 limit its use including pro-arrhythmic effects, thyroid disease, hepatotoxicity,  
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10 pulmonary toxicity and ophthalmological disorders.  
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14 Flecainide is a class 1c anti-arrhythmic<sup>8</sup>. It acts by blocking sodium channels to  
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16 reduce intracardiac conduction<sup>11</sup>. It has been associated with fatal arrhythmias in  
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18 patients with structural heart disease.  
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21  
22 Sotalol is a non-selective  $\beta$  blocker which also has class III anti-arrhythmic action<sup>8</sup>. It  
23  
24 leads to an increase in duration of the cardiac action potential and slows repolarisation  
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26 giving rise to a prolongation of the QT interval on ECG which may predispose to  
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28 ventricular arrhythmias<sup>12</sup>.  
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32 In this article we present a study using data from the General Practice Research  
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34 Database (GPRD) evaluating the adverse events and predictors of treatment  
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36 discontinuation in patients using these commonly prescribed anti-arrhythmic agents.  
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### 39 40 **Methods**

41  
42 We conducted a retrospective case control note review and outcome linkage analysis  
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44 on the GPRD routine clinical dataset to evaluate the adverse events and predictors of  
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46 treatment discontinuation in patients using licensed rhythm modifying medication  
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48 (amiodarone, flecainide and sotalol).  
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### Population for Analysis

The GPRD collects data from over 350 practices in the UK. More than three million patients are currently contributing data and the system has over 35 million patient years on record making it the largest primary care routine patient record database in the world. Information including patients demographics, diagnoses, prescribing history and test results are collected using VISION software and collated centrally. The GPRD has been widely used for pharmacoepidemiological research and data is quality assured by checks for consistency and completeness of data recording and adherence to GPRD guidelines<sup>13</sup>.

### Cases in this Linkage Study

Participants were 18 years and older with a diagnosis of atrial fibrillation. Patients were included in the study if they had a first prescription of rhythm modifying medication, namely amiodarone, flecainide or sotalol, at least 12 months after the start of GPRD data collection and a second prescription of the same drug within six months of the first. Follow-up of these patients began on the date of the second prescription, representing chronic rhythm medication users. Each amiodarone, flecainide and sotalol user was matched to three control patients by age (within 2 years), gender, practice and calendar time. Eligible controls had at least 12 months data prior to the start date. Patients with a record of AF or “non-specific heart rhythm disorders” were excluded as controls.

### Analysis

We evaluated the occurrence of known adverse events associated with amiodarone, flecainide and sotalol in patients on treatment compared with controls. For

1  
2 amiodarone we included hyperthyroidism and hypothyroidism, acute and chronic liver  
3 failure, pulmonary toxicity (pneumonitis or interstitial/alveolar pneumonitis), visual  
4 impairment (including blurred vision, visual halos, optic neuropathy or optic neuritis),  
5 congestive heart failure and all cause mortality. In the flecainide group we included  
6 acute and chronic liver disease, congestive heart failure and death. In the sotalol group  
7 we included hyperthyroidism and hypothyroidism, acute and chronic liver failure,  
8 congestive heart failure and all cause mortality.  
9

10  
11 The follow-up of all three groups was divided into current and past use. The periods  
12 of current use included the time from the date of a prescription for amiodarone,  
13 flecainide and sotalol until the expected end of treatment (based on the prescribed  
14 daily dose and number of tablets) plus an offset period. The period of offset was 2  
15 months for amiodarone and 1 month for sotalol or flecainide to take into account their  
16 different half lives. The period of past use was from the expected end of treatment  
17 plus the offset period until the end of the GPRD data collection or patients death,  
18 whichever came first. Patients taking amiodarone, flecainide or sotalol were censored  
19 if they switched treatment to another antiarrhythmic.  
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### 38 Statistical Methods

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40 We used Poisson regression to compare current users of amiodarone, flecainide and  
41 sotalol with past users and controls. Potential confounders included in the regression  
42 model were age, gender, body mass index, smoking history, alcohol use, history of  
43 ischaemic heart disease, heart failure, hypertension, cerebrovascular disease, diabetes  
44 mellitus, hyperthyroidism, prior drug use of statins, angiotensin receptor blockers and  
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2 oral glucocorticoids, number of GP visits prior in the six to twelve months prior to  
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4 index date and the socio-economic class of the practice region.  
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### 8 Data Mining Exercise

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10 We also conducted a data mining sensitivity analysis to explore any differences in  
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12 symptoms between those who stopped and those who continued treatment with  
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14 amiodarone, flecainide or sotalol. Each patient who discontinued treatment was  
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16 matched by age (within 5 years), gender and duration of treatment (<1 year, 1-3 years  
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18 3+ years) to one patient who continued treatment with the same drug. The symptoms  
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20 recorded between the last prescription and time of treatment discontinuation were  
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22 evaluated in patients who stopped treatment. A period of similar length was also  
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24 evaluated in those who continued treatment. Conditional logistic regression was used  
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26 to determine the symptoms most commonly reported by those stopping treatment  
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28 compared with those who did not.  
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### 31 Ethics

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33 The GPRD Group has ethical approval from a Multi-centre Research Ethics

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35 Committee (MREC) for all purely observational research using GPRD data; namely,  
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37 studies which do not include patient involvement, as here. No individual patients are  
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39 identifiable through this research.  
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### 43 Results

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45 A summary of the number and characteristics of patients involved in each analysis are  
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47 shown in table1.  
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	Amiodarone	Flecainide	Sotalol
Number of cases	8,229	1,335	5,365

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Number of controls	24,652	4,032	16,122
<u>Percentage age 65 and over (cases and controls)</u>	<u>50%</u>	<u>78%</u>	<u>63%</u>
Percentage male	57%	56%	50%
Taken drug less than 1 year	4,617 (56%)	867 (65%)	3,317 (62%)
Taken drug 1-3 years	2,250 (27%)	314 (24%)	1,308 (24%)
Taken drug for more than 3 years	1,362 (16.5%)	154 (11%)	740 (14%)

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Deleted: 52% under 70

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Table 1 – Patient characteristics by age, sex and drug duration

Adverse Outcomes Related to Amiodarone Use

As shown in table 2, congestive heart failure was more common in past users of amiodarone than controls. Risk was increased further in current users of amiodarone compared with controls. Risk of hyperthyroidism was increased more than 10 fold in past amiodarone users and more than 20 fold for current users. Hypothyroidism was also significantly more common in past users and higher still in current users. There were only a small number of cases of liver failure so further meaningful statistical analysis was not possible. Pulmonary toxicity was more common in past users and current users but this was not statistically significant. Visual impairment was not significantly different between exposed and unexposed groups either for past users of amiodarone nor current users. All-cause mortality was significantly higher in current amiodarone users than controls.

Results were not affected by excluding patients with an index date prior to 1996.

Adverse Outcomes Related to Flecainide Use

Congestive heart failure was more common in past users of flecainide compared with controls but not statistically significantly different in current users. All-cause mortality was increased three-fold in current users of flecainide compared with the

unexposed group. The number of cases of liver failure was small so statistical evaluation was not possible.

Excluding patients with an index date prior to 1996 did not alter these findings.

#### Adverse Outcomes Related to Sotalol Use

Congestive heart failure was more common in current users than controls and risk increased further for past users. All cause mortality was increased more than two-fold in the sotalol group. Hyperthyroidism was increased in current users and increased further in past users compared with controls. The risk of hypothyroidism was slightly increased in current users and further increased in past users of sotalol. The number of cases of liver failure was too small for analysis. There was no significant difference in pulmonary toxicity between exposed and unexposed groups for both past or current users.

Results were not affected by excluding patients with an index date prior to 1996.

Adverse effect	Amiodarone RR (95% CI)		Flecainide RR (95% CI)		Sotalol RR (95% CI)	
	Past user	Current user	Past user	Current user	Past user	Current user
All-cause mortality	4.48 (4.21-4.76)	-	3.01 (2.42-3.61)	-	2.61 (2.36-2.85)	-
Congestive heart failure	2.50 (2.08-2.91)	3.79 (3.22-4.36)	3.99 (2.18-5.81)	1.76 (0.90-2.62)	1.55 (1.21-1.88)	2.19 (1.71-2.67)
Hyperthyroidism	10.37 (6.63-14.11)	20.73 (13.74-27.72)	-	-	6.23 (3.11-9.35)	4.74 (2.36-7.12)
Hypothyroidism	2.33 (1.89-2.77)	9.00 (7.67-10.33)	-	-	2.35 (1.80-2.91)	1.35 (1.02-1.69)
Liver failure	NA	NA	NA	NA	NA	NA
Pulmonary toxicity	2.01 (0.62-3.40)	2.35 (0.81-3.88)	-	-	2.94 (-0.48-6.35)	1.34 (-0.33-3.01)
Visual impairment	0.94 (0.51-1.38)	1.62 (0.97-2.28)	-	-	-	-

Table 2 – Relative risk of adverse effects of amiodarone, flecainide or sotalol in cases compared with controls

### Data Mining Exercise

Possible causes for discontinuation of amiodarone by READ chapter included adverse effects, atrial fibrillation/flutter, hypertension, left ventricular failure and cardiac dysrhythmias. Reasons for cessation of flecainide included atrial fibrillation/flutter and adverse events. Reasons for sotalol discontinuation included dysrhythmias, atrial fibrillation/flutter, hypertension and adverse effects.

### Conclusions

#### *Summary of main findings*

Adverse events are much more common in patients currently or previously taking antiarrhythmics than age and gender matched controls, especially for amiodarone users. In patients with atrial fibrillation, all three antiarrhythmics were associated with increased all-cause mortality. Congestive heart failure was more common in all amiodarone and sotalol users as well as past users of flecainide. Thyroid disease was more common in patients treated with amiodarone and sotalol but only amiodarone had an increased risk of pulmonary toxicity. The number of patients with liver failure was too small in all cases for statistical analysis.

The adverse events arising in patients treated with amiodarone, flecainide and sotalol were similar to the reasons given for discontinuation of treatment in the data mining exercise.

Congestive heart failure is a risk factor for AF<sup>11</sup> so this association in [the amiodarone and sotalol](#) groups was not surprising. Also, some guidelines suggest rhythm rather

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2 than rate-control is the preferred treatment for congestive heart failure further  
3 explaining the increased risk seen in patients taking rhythm-control agents compared  
4 to control<sup>27</sup>. Flecainide is contraindicated in patients with structural or functional heart  
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6 disease and there was no significant difference in heart failure between cases and  
7 controls in current flecainide users. Amiodarone has a causal link with thyroid disease  
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9 and pulmonary toxicity however a causal association between sotalol and thyroid  
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11 disease has not previously been well recognised.  $\beta$  blockers are used to manage  
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13 patients with hyperthyroidism which may explain this association although the reason  
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15 for an increased incidence of hypothyroidism in patients taking sotalol is less clear.  
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### 22 *Strengths and limitations of the study*

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24 The GPRD is a large well-validated database containing information on patients from  
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26 wide demographic backgrounds. The system allows complex analyses of adverse  
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28 events recorded in patients with atrial fibrillation and receiving anti-arrhythmic  
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30 medications.  
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34 The criterion for diagnosis of AF was unclear and may have been on clinical grounds,  
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36 by electrocardiogram or by a specialist but this is impossible to elucidate from the  
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38 GPRD system. There may also be a significant time interval between the time data  
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40 was recorded to the time of this study and clinical practice may have changed during  
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42 this period, however, analysis excluding data prior to 1996 did not significantly alter  
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44 the results.  
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49 The study compared patients with atrial fibrillation taking antiarrhythmic medications  
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51 with controls who both did not have AF and were not taking antiarrhythmic  
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2 medications. There is a well recognised excess mortality in all patients with AF<sup>4</sup>  
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4 which may explain some of this result, furthermore, patients treated with rhythm  
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6 rather than rate control may have worse prognosis disease. However, at least some of  
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8 this effect could also be due to malignant side effects of anti-arrhythmic medications.  
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11  
12 The number of patients with liver failure was too small for meaningful analysis  
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14 however it may have been interesting to examine the liver function tests in cases and  
15  
16 controls to see if there was a difference between the two groups.  
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### 18 19 20 *Comparison with existing literature*

21  
22 The study showed a significantly higher rate of adverse events in patients taking  
23  
24 rhythm control agents compared with controls. The side effect profile of  
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26 antiarrhythmic agents, particularly amiodarone, has been well described in existing  
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28 literature.  
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### 30 31 32 **Amiodarone**

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#### 33 34 Proarrhythmic effects

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36 Prolongation of the QT interval in patients taking amiodarone can predispose to  
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38 torsade de pointes (TdP), polymorphic ventricular fibrillation, which can be fatal. The  
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40 incidence of TdP in patients prescribed amiodarone is however less than 1%<sup>14</sup>. The  
41  
42 risk of TdP is increased in the presence of electrolyte abnormalities or concurrent pro-  
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44 arrhythmogenic medications<sup>15</sup>. The most common arrhythmia associated with  
45  
46 amiodarone use is bradycardia which can be profound in older patients with a history  
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48 of ischaemic heart disease and may require pacing<sup>16</sup>. Arrhythmic events could partly  
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50 explain the excess mortality in patients receiving amiodarone.  
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### Thyroid disease

Amiodarone is associated with thyroid disorders which can range from subclinical abnormalities found on thyroid function tests to clinically apparent hypo- and hyperthyroidism<sup>17</sup>. Hypothyroidism is more common in women and patients with antithyroid antibodies<sup>18</sup>, however, in a sub-study of the Sotalol Amiodarone Atrial Fibrillation Efficacy Trial (SAFE-T) involving mostly male patients with an average age of 67 years, subclinical hypothyroidism was seen in 25.8% of patients treated with amiodarone compared with 6.6% of controls (p<0.0001) and clinically significant hypothyroidism was found in 5.0% of amiodarone treated patients compared with 0.3% of controls (p<0.001). There was no statistically significant difference in hyperthyroidism in this subgroup between amiodarone-treated patients and controls<sup>19</sup> however, elsewhere estimates of hyperthyroidism range from 1 to 23% in patients taking amiodarone<sup>20</sup>. In this study, patients receiving amiodarone were twenty times more likely to have hyperthyroidism than controls.

### Hepatotoxicity

The cases of liver failure were small in number in this study precluding meaningful statistical analysis however other studies have shown that elevated liver enzymes are seen in 15-30% of patients taking amiodarone and annual incidence of hepatitis and cirrhosis is around 0.6%<sup>21</sup>. This is more common in patients on high doses of amiodarone but has been reported in those receiving low dose oral therapy<sup>22</sup>.

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### Pulmonary toxicity

Amiodarone pulmonary toxicity (APT) is estimated to occur in 5-7% of patients receiving amiodarone. Mortality is approximately 5-10%<sup>23</sup>. It is most common amongst patients undergoing cardiac surgery who are receiving high doses of amiodarone to prevent ventricular arrhythmia however APT has also been seen in patients following lower doses of oral treatment<sup>24</sup>.

#### Ophthalmological Disorders

Corneal deposits are seen in up to 100% of patients receiving amiodarone. These rarely impair vision. Optic neuritis has also been associated with amiodarone therapy although a causal link is not certain<sup>25</sup>. This occurs in less than 1% of patients and routine retinal screening has not been shown to be beneficial<sup>26</sup>. [This is consistent with the findings of this study which did not show a significant difference in visual impairment between those receiving amiodarone and controls.](#)

Amiodarone is recommended in the National Institute of Health and Clinical Excellence (NICE) guidelines for use in atrial fibrillation only after failure of other treatments<sup>27</sup> and is most commonly initiated by a specialist. The routine tests recommended for monitoring of patients are shown in table 3.

Adverse effect	Test	Frequency
Arrhythmia	Electrocardiogram	At baseline Every 12 months
Hypo/hyperthyroidism	Thyroid function tests	At baseline Every 6 months
Hepatotoxicity	Liver function tests	At baseline Every 6 months
Pulmonary toxicity	Chest x-ray	At baseline Every 12 months
Ophthalmological disorders	Ophthalmological examination	At baseline if pre-existing visual impairment If symptoms occur

Table 3 – Routine testing in patients receiving amiodarone<sup>28</sup>

### Flecainide

Flecainide was found to increase mortality in patients with a history of myocardial infarction and asymptomatic or mild ventricular arrhythmias in the Cardiac Arrhythmia Suppression Trial (CAST) study<sup>29</sup>. As a result of these findings, flecainide is contraindicated in patients with structural heart disease [in clinical practice](#). The drug does however have a role as “pill-in-the-pocket” therapy for those with known paroxysmal AF. In this approach to treatment, patients with at least one episode of previously documented AF carry a single dose of flecainide with them and take the medication at the onset of symptoms. A study of 165 patients with a total of 618 AF episodes presenting with sudden onset of palpitations without haemodynamic compromise (systolic BP 100 or more and mean heart rate of greater than 70) found that 94% of episodes were terminated by flecainide within a mean time of 113 minutes. Side effects were infrequent with one episode of rapid atrial flutter and 11 cases of non-cardiac side effects including nausea, vertigo and asthenia<sup>30</sup>.

Flecainide is also indicated for rhythm control in persistent AF in patients with a structurally normal heart<sup>27</sup>. A systematic review, which included 5 trials involving flecainide following cardioversion, found a reduction in recurrence rate of AF. There was however an increase in withdrawal of treatment in the flecainide groups compared with control due to side effects including proarrhythmic events<sup>31</sup>.

Flecainide can be fatal in overdose, due to widening of the QRS complex and prolongation of the PR interval seen on ECG predisposing to ventricular tachycardia or bradycardic episodes requiring pacing<sup>32 33</sup>.

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## Sotalol

In the Sotalol Amiodarone Atrial Fibrillation Efficacy Trial (SAFE-T), amiodarone and sotalol were found to have equivalent efficacy for conversion to sinus rhythm (27.1% v 24.2%, p=0.45) but amiodarone was superior in maintaining sinus rhythm (median time to recurrence of AF 487 days v 74 days, p<0.001) except in patients with ischaemic heart disease where both drugs were equivalent. Sotalol was more efficacious than placebo in all groups<sup>34</sup>.

The main cardiovascular side effect of sotalol relates to prolongation of the QT interval which can predispose to torsade de pointes<sup>35</sup>. In a systematic review of 9 studies comparing sotalol with control, there was an increased risk of proarrhythmic events in the sotalol groups (OR 2.20, 95% CI 1.31-3.69)<sup>31</sup>. [This could partly explain the excess mortality seen in patients receiving sotalol in the study.](#)

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In a substudy of the AFFIRM trial, adverse events causing discontinuation of treatment in the 135 patients in the sotalol arm included congestive heart failure (2.2%), bradycardia (2.2%), gastrointestinal events (4.4%), pulmonary events (0.7%) and syncope (0.7%)<sup>36</sup>. Another study investigating long term efficacy and safety of sotalol in 106 patients found 22% had tolerable side effects such as gastrointestinal discomfort (2%), neurological disturbance (11%), asymptomatic bradycardia (7%) and general weakness (2%). A further 10% discontinued treatment due to significant adverse effects, 4% of these were due to proarrhythmic events and the remainder were due to asymptomatic QT prolongation, congestive heart failure, symptomatic bradycardia and gastrointestinal events.

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4 Adverse events associated with antiarrhythmic agents are commonly described in the  
5 literature as discussed above, however, they continue to be commonly prescribed. A  
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8 Canadian study looking at drug use in 465 patients with new onset AF found that  
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10 36.4% (92/253) of patients taking sotalol and 64.1% (25/39) of patients taking  
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12 amiodarone had contraindications or warnings. The number of patients taking  
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14 flecainide was small but 33% (2/6) patients also had contraindications or warnings<sup>37</sup>.  
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#### 17 18 *Implications for future research and practice*

19  
20 Atrial fibrillation is increasingly common as the population ages and survival from  
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22 ischaemic heart disease improves. AF guidelines recommend rhythm-control agents  
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24 for younger patients, those who are symptomatic, present for the first time with lone  
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26 AF or have congestive heart failure<sup>27</sup>. However, the AFFIRM study found no  
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28 mortality benefit from rhythm control compared to rate control and a higher rate of  
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30 adverse events in patients taking rhythm control agents. Further research is required to  
31  
32 establish the benefit-risk ratio of rhythm-control treatments in the subgroups of  
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34 patients recommended to receive these agents. Patients with atrial fibrillation should  
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36 be carefully counselled about potential adverse effects before starting rhythm-control  
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38 agents both to allow informed consent and ensure symptoms of adverse events are  
39  
40 recognised and reported by the patient early to allow discontinuation or change of  
41  
42 treatment as required.  
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#### 45 46 47 48 *Funding body*

49  
50 Sanofi-Aventis funded the original study design and GPRD costs and associated  
51  
52 analysis but were not involved in interpreting, writing, reviewing or editing the paper.  
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