James A Hodgkinson, Clare J Taylor and FD Richard Hobbs

Predictors of incident atrial fibrillation and influence of medications:

a retrospective case–control study

Abstract

Background
Atrial fibrillation (AF) is a common condition, associated with raised mortality and risk of major morbidity, and is predicted to increase due to an aging population.

Aim
To update earlier research of AF predictors using UK data.

Design and setting
Case–control analysis of adults aged 18 years and older with a diagnosis of AF in practices registered with the General Practice Research Database (GPRD) in the UK.

Method
Using the GPRD, a case–control analysis was performed using logistic regression to compare 55 412 incident AF cases to 216 400 controls, for medical history and prior use of drugs. The association between time since start of diagnosis or drug use and AF risk was summarised using Spline regression.

Results
The following were confirmed as risk factors for AF: heart failure (risk ratio [RR] 2.91 [95% CI = 2.59 to 3.27]); ischaemic heart disease (IHD) (RR 2.00 [95% CI = 1.78 to 2.24]); hypertension (RR 2.60 [95% CI = 2.32 to 2.92]); hyperthyroidism (RR 1.56 [95% CI = 1.39 to 1.75]); being a heavy drinker (RR 1.43 [95% CI = 1.27 to 1.60]); cerebrovascular accident (RR 1.48 [95% CI = 1.32 to 1.66]); and obesity (body mass index ≥30 kg/m^2 RR 1.29 [95% CI = 1.15 to 1.45]). Current use of oral glucocorticoids (RR 1.62 [95% CI = 1.44 to 1.82]) and of beta-2 agonists (RR 1.30 [95% CI = 1.16 to 1.46]) were identified as significant risk factors, and statins (RR 0.82 [95% CI = 0.73 to 0.92]) as a significant protective factor. No effect was found for current use of bisphosphonates (RR 0.95 [95% CI = 0.85 to 1.07]), renin–angiotensin–aldosterone system (RAAS) agents (RR 1.04 [95% CI = 0.93 to 1.17]), or xanthine derivatives (RR 1.09 [95% CI = 0.97 to 1.22]). Spline regression analysis found the effect of heart failure, IHD, use of oral glucocorticoids, and use of statins on the likelihood of developing AF was sustained over a number of years.

Conclusion
These findings update the risk factors that are associated with AF, and confirm the protective properties of statins and the risks of beta-2 agonists in developing AF, but not the supposed protective qualities of glucocorticoids and RAAS agents.

Keywords
atrial fibrillation; database; epidemiology; general practice; pharmacology; risk factors.

INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia. The prevalence of AF in the UK is more than 12/1000, increasing to over 100/1000 in people aged 85 years and over;[1] 16% of this age group had AF in the Screening for Atrial Fibrillation in the Elderly (SAFE) study.[2] Furthermore, AF is a major independent risk factor for stroke[3] and heart failure,[4] and is associated with increased morbidity and mortality.[5]

AF and medical risk factors

The Framingham Heart Study found diabetes, hypertension, congestive heart failure, and valve disease were significantly associated with risk for AF.[6] The Cardiovascular Health Study identified a history of congestive heart failure, valvular heart disease and stroke, echocardiographic evidence of enlarged left atrial dimension, abnormal mitral or aortic valve function, treated systemic hypertension, and advanced age as independently associated with AF.[7] These findings have since been replicated worldwide (Table 1) in China,[8] Spain,[9–12] US,[13–15] Italy,[16] and Sweden.[17] Evidence of the risk of AF in hyperthyroidism has been found in the Cardiovascular Health Study,[18] a UK population-based study,[19] a systematic review,[20] and earlier research using the General Practice Research Database (GPRD).[21]

AF and lifestyle risk factors

There is an increased risk of developing AF for patients with a body mass index (BMI) of 30 kg/m^2 or more and alcohol consumption of over 42 units a week.[21] One meta-analysis demonstrated that obesity increased the risk of developing AF by 49% in the general population, and the risk escalated in parallel with increased BMI.[22]

AF: pharmacological risk and protective factors

Evidence for the influence of drugs on AF is generally less conclusive, though expanding. Most evidence has been reported for four classes of agent: meta-analyses report potentially clinically important reductions in AF incidence with drugs acting on the renin–angiotensin–aldosterone system (RAAS) and with statins; possible modest reductions in AF onset with oral glucocorticoids (but from small series only); and potentially greater incidence with beta-agonist use.

Oral glucocorticoids

Evidence of the effect of glucocorticoids on AF is focused on protecting against postoperative AF. Methylprednisolone reduced permanent AF from 29% in a placebo group to 2% in a glucocorticoid group,[23] and decreased AF incidence (P= 0.020).[24] Dexamethasone was associated with a lower incidence of new-onset AF in post hoc analysis,[25] but this was not replicated in a subsequent randomised controlled trial (RCT).[26] One RCT found the incidence of postoperative AF was significantly lower in a hydrocortisone group (30%) than in a placebo group (48%) after

JA Hodgkinson, BA, MSc, PhD, research fellow; **CJ Taylor**, MA, MRCP, DCH, MPH, research fellow; **FDR Hobbs**, FRCGP, FRCP, FESC, FMedSci, professor and head of school of health and population sciences, Department of Primary Care Clinical Sciences, School of Health and Population Sciences, University of Birmingham.

Address for correspondence
Dr James Hodgkinson, Department of Primary Care Clinical Sciences, School of Health and Population Sciences, University of Birmingham, Edgbaston, Birmingham, B15 2TT.

E-mail:j.a.hodgkinson@bham.ac.uk

Submitted: 10 June 2010; **Editor's response:** 13 July 2010; **final acceptance:** 30 September 2010.

This is the full-length article (published online 31 May 2011) of an abridged version published in print. Cite this article as: **Br J Gen Pract 2011; DOI: 10.3399/bjgp11X578034.**

How this fits in

A range of medical and lifestyle risk factors for atrial fibrillation (AF) were known to exist, and are confirmed by this study in a large UK population. This study provides additional evidence on the AF risk or protection offered by various pharmacoepidemiological factors. As the number of patients with AF is likely to increase without appropriate prevention strategies as the population ages, a thorough understanding of the risks associated with the use of specific drugs will be essential in treating not only patients with existing AF, but those whose treatment for other conditions may put them at risk for, or protect them from, developing AF.

cardiac surgery ($P = 0.004$).[27] A meta-analysis of RCTs found the risk of postoperative AF was reduced by 50% by the use of perioperative corticosteroids.[28] A population-based case–control study in Denmark with over 20 000 cases and 200 000 controls[29] found that current glucocorticoid use, but not past use, was associated with an almost twofold increased risk of AF or flutter, supporting the findings of two much smaller case–control studies in the Netherlands[30] and the UK.[31]

Beta-2 agonists

The use of beta-2 agonists has been associated with tachycardia, abnormal electrocardiogram results, and AF.[32] A meta-analysis of the cardiovascular effects of beta-2 agonists in patients with asthma and chronic obstructive pulmonary disease (COPD) concluded that beta-2 agonist use increases the risk for adverse cardiovascular events (including AF), as the initiation of treatment increases heart rate and reduces potassium concentrations compared to placebo.[33] However, in a more recent large RCT of COPD patients, long-acting beta-2 agonists did not lead to an increase in more serious arrhythmias.[34] Conversely, the use of beta-blockers was inversely correlated with AF (odds ratio [OR] 0.54) in 1401 patients with myocardial infarction,[35] and in UK GPRD hypertensive patients (OR 0.78 [95% confidence interval {CI} = 0.67 to 0.92]),[36] but in a US case–control study in a general hypertensive population without heart failure, single drug-use of beta-blockers was not significantly associated with lower AF risk (OR 1.05 [95% CI = 0.73 to 1.52]).[37]

Statins

Meta-analyses on the preventative effects of statins on AF have provided distinct results depending on the selection of studies themselves using heterogeneous patient populations. Statin use reduced the odds of developing AF by 45% across 14 trials,[38] or 61% in six studies.[39] However, other meta-analyses found the association depended on the methodology of trials selected, with a reduced risk of AF in observational studies but not RCTs,[40] and in hypothesis-generating but not hypothesis-testing trials.[41]

Individual RCTs show a range in the strength of effect of statin usage, with the relative risk (RR) of AF reduced by 28% and 13% respectively for the Sudden Cardiac Death in Heart Failure Trial[42] and the Gruppo Italiano per lo Studio della Sopravivvenza nell'Insufizzienza Cardiaca — Heart Failure[43] (rosuvastatin only) populations, the latter only being statistically significant compared to placebo after adjustment for clinical variables and concomitant therapy. An RCT of 200 patients undergoing cardiac surgery showed atorvastatin decreased the incidence of postoperative AF by 61%;[44] a smaller trial also found this after electrical cardioversion,[45] but another found that pravastatin did not reduce AF recurrence.[46]

RAAS agents

A meta-analysis found treatment with angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) reduced the RR of AF in patients by 19% ($P<0.001$).[47] In two case–control studies of patients with hypertension, single-drug users of ACEIs or ARBs had a lower risk of AF compared to single-drug users of diuretics (OR 0.63 [95% CI = 0.44 to 0.91])[37] or of calcium-channel blockers (ACEIs OR 0.75 [95% CI = 0.65 to 0.87]; ARBs OR 0.71 [95% CI = 0.57 to 0.89]).[36] The rate of acute recurrence of AF was lower in a RAAS group compared to controls (17% versus 31%, $P = 0.026$) in patients with AF scheduled for electric cardioversion.[48]

Bisphosphonates

Bisphosphonate use (specifically zoledronate and alendronate) has been reported as a risk factor for AF in women.[49–51] However a case–control study using the GPRD between 2004 and 2006 found no robust evidence of long-term increased risk of AF and flutter in women exposed to oral bisphosphonates (age-adjusted incident rate ratio 1.07 [95% CI = 0.94 to 1.21]), although it could not exclude the possibility of an increase in risk during the first few months of therapy with

Table 1. Medical risk factors identified from previous research

Study reference number	Country	*N*	Ages, mean years unless stated	Sex, female/male, %	Risk factors (95% CI)					
					Heart failure	Hypertension	Coronary heart disease	Valvular disease	Diabetes	Hyperthyroidism
7	US	4731	Range 55–94	55.8/44.2	F OR 5.9;	F OR 1.4; M OR 4.5	NR M OR 1.5	F OR 3.4;	F OR 1.6; M OR 1.8	NR M OR 1.4
9	China	9297	65.5 (range 18–99)	48/52	33.1%	40.3%	34.8%	23.9%	4.1%	2.5%
10	Spain	7108 (AF 605)	71.9 (all ≥60)	53.6/46.4	NR	Model 1, OR 2.53 (1.60 to 4.01)	Model 1, OR 3.69 **(3.03 to 4.51)**[a]	NR	Model 1 NS; model 2 OR 1.18 (0.97 to 1.44)	NR
11	Spain	836 (263)[b]	HF 63.4 versus no HF 59.9	19.9/80.1	12.3% versus 5.1%	NR	NR	NR	NR	NR
12	Spain	32 051 (AF 6194)	68.4	AF only: 45.8/54.2	33%	25%	12%	NR	NR	NR
13	Spain	1000 (AF 300)	AF 66 (SD 8), control 64 (SD 12)	AF only: 52.3/47/7	OR 2.1 (1.2 to 3.3)	OR 1.7 (1.2 to 2.3)	OR 1.8 (1.2 to 2.6)	OR 2.2 (1.4 to 2.5)	OR 1.9 (1.2 to 2.9)	NS (4% of AF group)
14	US	3983	72 (SD 5)	0/100	RR 3.37 (2.29 to 4.96)	RR 1.42 (1.10 to 1.84)	NR	RR 3.15 (1.99 to 5.00)	NR	NR
15	US	2796 (AF 347)	AF 69 (SD 10), control 62 (SD 12)	33/67	41% versus 9% (P<0.001)	56% versus 56% (NS)	71% versus 74% (NS)	NR	24% versus 17% (P<0.05)	NR
16	US	581 (AF 42)	AF 82 (SD 10), control 66 (SD 13)	AF: 45.2/54.8; control: 50.6/49.4	21.4% versus 2.6% (P<0.001)	66.7% versus 53.4% (P = 0.1)	35.7% versus 11.7% (P = 0.001)	NR	14.3% versus 8.9% (P = 0.27)	NR
17	Italy	694	71 (SD 9)	44.8/55.2	23%	58%	NR	NR	NR	NR
18	Sweden	7495 (AF 754)	47–55 (follow-up 25.2 years)	0/100	OR 6.77 (5.17 to 8.87)[c]	OR 1.33 (1.07 to 1.65)	OR 6.77 (5.17 to 8.87)[b]	NR	NS (P>0.01)	NR
19	US	3233	72.7 (all ≥65)	59.6/40.4	NR	NR	NR	NR	NR	HR 1.98 (1.29 to 3.03)
20	UK	5859	Median 72, range 65–98	50.9/49.1	OR 3.75 (2.15 to 6.52)	OR 1.39 (1.08 to 1.80)	NR	NR	OR 2.02 (1.44 to 2.84)	OR 1.89 (1.01 to 3.57)
22	UK	6035 (AF 1035)	Range 40–89	54/46	RR 3.6 (2.7 to 4.7)	RR 1.8 (1.5 to 2.1)	RR 1.3 (1.0 to 1.6)[d]	RR 4.3 (2.6 to 6.9)	RR 0.8 (0.6 to 1.1)	RR 2.7 (1.5 to 5.1)

AF = atrial fibrillation. F = female. HF = heart failure. HR = hazard ratio. M = male. NR = not reported. NS = not significant. OR = odds ratio. RR = risk ratio. SD = standard deviation. Where two figures are presented separated by versus, the first figure is always the AF group and the second the control group unless otherwise stated. [a]Established cardiovascular disease. For model 2, the OR = 4.08 (95% CI = 3.36 to 4.97). [b]Patients with heart failure. [c]Heart failure or coronary heart disease. [d]Ischaemic heart disease.

alendronic acid.[52] In a meta-analysis of four RCT datasets, bisphosphonate exposure was significantly associated with risk of serious AF adverse events (OR 1.47 [95% CI = 1.01 to 2.14]) but not all AF events (OR 1.14 [95% CI = 0.96 to 1.36]).[53] In two large prospective databases, there was no increased risk of AF for patients treated with bisphosphonates, and patients who received bisphosphonates were older and had more cardiovascular disease, which the authors suggested may account for the increased arrhythmia risk reported in other studies.[54] Other systematic reviewers found non-significantly higher risk both of overall (OR 1.18 [95% CI = 0.84 to 1.66]) and serious AF (OR 1.59 [95% CI = 0.61 to 3.75]) in bisphosphonate-treated patients across identified RCTs.[55]

Xanthine derivates

Evidence on the effect of xanthine derivates is limited. In a case–control study of a range of medications used to treat respiratory diseases, the risk of AF was increased for theophyllines, with a weak association especially found in short-term use (RR 1.8 [95% CI = 0.9 to 3.7]).[56]

METHOD

Study population

To explore associations in a prospective case–control study, GPRD routine clinical data were used. The GPRD is the world's largest computerised database of anonymised longitudinal patient records from primary care, and currently collects data from around 450 practices on 3.6 million active patients in the UK. Data are quality assured by checks for consistency and completeness of data recording and adherence to GPRD guidelines. Epidemiological studies have confirmed the validity and data completeness of the GPRD.[57] A total of 55 412 AF cases and 216 400 controls were identified in the GPRD (Table 2).

All practices that collected data and were

Table 2. Patient demographics

Characteristic	Cases, *n* (%), total *n* = 55 412	Controls, *n* (%), total *n* = 216 400
Sex		
Female	27 451 (49.5)	107 505 (49.7)
Male	27 961 (50.5)	108 895 (50.3)
Age, years		
18–39	722 (1.3)	2879 (1.3)
40–64	9678 (17.5)	38 495 (17.8)
65–69	5974 (10.8)	23 678 (10.9)
70–74	8621 (15.6)	34 020 (15.7)
75–79	10 595 (19.1)	41 597 (19.2)
80–84	9992 (18.0)	38 865 (18.0)
85–115	9830 (17.7)	36 866 (17.0)
Mean age (SD)	74.0 (11.9)	73.8 (11.8)
$CHADS_2$ score		
0	8190 (14.8)	59 879 (27.7)
1	17 340 (31.3)	75 199 (34.8)
2	16 475 (29.7)	51 877 (24.0)
3	8194 (14.8)	17 810 (8.2)
4	3672 (6.6)	8951 (4.1)
5	1376 (2.5)	2439 (1.1)
6	165 (0.3)	245 (0.1)
Mean $CHADS_2$ (SD)	1.8 (1.2)	1.3 (1.2)

up to standard (UTS), as defined by the database providers and based on internal checks of the completeness and continuity of recording for GPRD, were eligible for inclusion.

The study drew on data from the whole database from 1987 (though most records are from 1990 onwards). Each patient was followed over their entire UTS period registered at the practice, from their registration date or the date the practice became UTS (whichever came latest) until their transfer-out date or last data-collection date for that practice. Data extraction was carried out in May 2007 using the most up-to-date data. A sensitivity analysis excluding patients with an index date prior to 1996 was also conducted, to ascertain if growing awareness of AF and understanding of the condition had impacted on UK treatment and GP recording practice.

Case definition

Cases were adults aged 18 years and older with a new diagnosis of AF during GPRD data collection. Patients with a history of heart valve problems and/or replacement surgery were excluded from the analysis. Each AF patient was matched to at least three control patients by age (within 2 years), sex, practice, and calendar time. Eligible control practices had at least 12 months' data prior to this date. Patients with a record ever of AF or non-specific heart rhythm disorder before or during the study period were excluded as control patients.

Incident AF cases were defined as having a first record of AF (by Read code) at least 12 months after start of follow-up, without any history of non-specific codes for heart rhythm disorders and without any prior use of oral anticoagulants. The researchers tried to exclude those patients that may have had AF before entering the study period and were not appropriately coded; therefore, all patients with a non-specific code for heart rhythm disorders were excluded from the study.

Analysis of risk

All predictors evaluated are shown in Table 3. Prior use of medication was classified as current, recent, or past (current use of drugs defined as prescribing in the 3 months before the index date, recent 3–12 months prior, and past use more than12 months ago). Estimates of RR of incident AF for each of the given factors were computed using stepwise conditional logistic regression, adjusted firstly by age and sex, and then fully adjusted for all covariates.

The association between AF and time since the start of the disease or the start of drug therapy was evaluated. Spline regression (advocated as an alternative to categorical analysis[58]) was used to summarise the association between time since start of diagnosis or drug use and the AF risk.

Table 3. Distribution of different characteristics among atrial fibrillation (AF) cases and controls: relative risk (RR) of developing AF, fully adjusted

	AF cases (%), *n* = 55 412	Controls (%), *n* = 216 400	Adjusted RR (95% CI)
COPD	3334 (6.0)	8488 (3.9)	1.05 (0.94 to 1.18)
Cerebrovascular accident	7070 (12.8)	17 217 (8.0)	1.48 (1.32 to 1.66)
Diabetes	5636 (10.2)	18 427 (8.5)	0.86 (0.77 to 0.96)
Heart failure	10 077 (18.2)	12 294 (5.7)	2.91 (2.59 to 3.27)
Hyperthyroidism	1189 (2.1)	2717 (1.3)	1.56 (1.39 to 1.75)
Ischaemic heart disease	14 993 (27.1)	34 610 (16.0)	2.00 (1.78 to 2.24)
No hypertension[a]	18 252 (32.9)	117 031 (54.1)	0.40 (0.36 to 0.45)
Bisphosphonates[b]			
Not used	52 980 (95.6)	208 277 (96.2)	1
Past	629 (1.1)	2119 (1.0)	0.99 (0.88 to 1.11)
Recent	411 (0.7)	1226 (0.6)	1.08 (0.96 to 1.21)
Current	1392 (2.5)	4778 (2.2)	0.95 (0.85 to 1.07)
Oral glucocorticoids[b]			
Not used	45 908 (82.8)	189 404 (87.5)	1
Past	4410 (8.0)	15 226 (7.0)	0.95 (0.85 to 1.07)
Recent	1509 (2.7)	4656 (2.2)	0.99 (0.88 to 1.11)
Current	3585 (6.5)	7114 (3.3)	1.62 (1.44 to 1.82)
Statins[b]			
Not used	47 100 (85.0)	191 919 (88.7)	1
Past	571 (1.0)	1943 (0.9)	0.84 (0.75 to 0.94)
Recent	597 (1.1)	1629 (0.8)	0.94 (0.84 to 1.05)
Current	7144 (12.9)	20 909 (9.7)	0.82 (0.73 to 0.92)
Xanthine derivate[b]			
Not used	52 729 (95.2)	209 074 (96.6)	1
Past	1409 (2.5)	4430 (2.0)	0.87 (0.78 to 0.98)
Recent	273 (0.5)	662 (0.3)	1.04 (0.93 to 1.17)
Current	1001 (1.8)	2234 (1.0)	1.09 (0.97 to 1.22)
Beta-2 agonists[b]			
Not used	42 482 (76.7)	179 440 (82.9)	1
Past	4090 (7.4)	13 820 (6.4)	1.07 (0.95 to 1.20)
Recent	1873 (3.4)	6002 (2.8)	1.06 (0.94 to 1.19)
Current	6967 (12.6)	17 138 (7.9)	1.30 (1.16 to 1.46)
Drugs affecting the renin–angiotensin–aldosterone system[b]			
Not used	39 412 (71.1)	178 435 (82.5)	1
Past	2196 (4.0)	6525 (3.0)	0.92 (0.82 to 1.03)
Recent	1121 (2.0)	2609 (1.2)	0.97 (0.86 to 1.09)
Current	12 683 (22.9)	28 831 (13.3)	1.04 (0.93 to 1.17)
Alcohol consumption			
No	7207 (13.0)	28 290 (13.1)	1
Ex-drinker	2384 (4.3)	7917 (3.7)	1.11 (0.99 to 1.25)
Yes	32 320 (58.3)	115 837 (53.5)	1.15 (1.02 to 1.29)
Unknown	13 501 (24.4)	64 356 (29.7)	1.11 (0.99 to 1.25)
Heavy drinker	1409 (2.5)	3586 (1.7)	1.43 (1.27 to 1.60)
Smoking			
No	26 381 (47.6)	97 930 (45.3)	1
Ex-smoker	13596 (24.5)	43 821 (20.3)	1.02 (0.91 to 1.14)
Yes	7354 (13.3)	30 845 (14.3)	0.89 (0.79 to 1.00)
Unknown	8081 (14.6)	43 804 (20.2)	0.80 (0.71 to 0.90)
Body mass index (kg/m^2)			
10–19	2995 (5.4)	10 855 (5.0)	1.14 (1.09 to 1.19)
20–24	14 578 (26.3)	59 568 (27.5)	1
25–29	16 750 (30.2)	63 334 (29.3)	1.02 (0.91 to 1.14)
≥30	10 025 (18.1)	27 347 (12.6)	1.29 (1.15 to 1.45)
Unknown	11 064 (20.0)	55 296 (25.6)	0.86 (0.77 to 0.96)

COPD = chronic obstructive pulmonary disease. [a] 'No hypertension' is defined as systolic blood pressure (BP) below 140/90 mmHg, and excludes those with unknown or equivocal BPs. For patients with high BP measurements, a minimum of two above-normal BP measurements within 6 months of each other were required and these values were averaged (hence the possibility of the category 'equivocal'). For those with normal BP measurements, only a single measurement was required. In the case of no recent record of BP measurement, BP was included as a missing value into the logistic regression analysis. [b]Prior use of medication was classified as current, recent, or past (current use of drugs defined as prescribing in the 3 months before the index date, recent 3–12 months prior, and past use more than 12 months ago).

RESULTS

This analysis included 55 412 cases and 216 400 controls. Some demographic differences were found between cases and their controls. AF cases had (inevitably) higher $CHADS_2$[59] scores than the controls (mean $CHADS_2$ for cases was 1.76 [standard deviation {SD} 1.24] and for controls 1.30 [SD 1.16]), were more likely to be obese, and less likely to be smokers than their matched controls. Table 3 shows the distribution of health-related characteristics in both cases and controls, including the fully adjusted RRs (adjusted for all covariates analysed in Table 3 and $CHADS_2$ score) of developing AF.

As Table 3 shows, a strong association was found between AF and history of heart failure, ischaemic heart disease (IHD), current use of oral glucocorticoids, hyperthyroidism, cerebrovascular accident (CVA), being a heavy drinker, use of beta-2 agonists, and BMI ≥30 kg/m^2. There was no association identified between AF and any use of bisphosphonates or RAAS agents, current use of xanthine derivates, or history of chronic obstructive pulmonary disease (COPD).

Absence of hypertension, diabetes, use of statins, and being a current smoker had an apparently protective effect. Diabetes mellitus and smoking have previously been indicated as independent risk factors for stroke, so these findings appear counterintuitive (though both are only marginally statistically significant). There may be recording bias concerning smoking and alcohol data, as GPs would be more likely to ask about alcohol intake and smoking status in AF patients compared to non-AF patients. It is possible there may be a 'survivor effect' whereby those still alive with diabetes or currently smoking may be less likely to develop AF.

Near-identical results were found when patients with an index date prior to 1996 were excluded, except for smoking and beta-2 agonists. The fully adjusted RR for current smokers rose to 1.31 (95% CI = 1.17 to 1.47), showing that in this group smoking is a significant risk factor for developing AF. This provides some support for the hypothesis that the apparent protective effect of smoking when patients with an index date prior to 1996 are included is indeed a 'survivor effect'. (However, the result for diabetes is little different from that for the entire dataset.)

Oral glucocorticoids

The RR of incident AF for current use of oral glucocorticoids was estimated at 1.62 (95% CI = 1.44 to 1.82). The pattern for recent and past use of oral glucocorticoids was different: a significant but very weak beneficial effect was found for past use and no effect for recent use.

Funding body
Sanofi-Aventis funded the GPRD costs and associated analysis but were not involved in interpreting, writing, reviewing, or editing the paper.

Ethics committee
The GPRD Group has ethical approval from a multicentre research ethics committee for all purely observational research using GPRD data. No individual patients are identifiable through this research.

Provenance
Freely submitted; externally peer reviewed.

Competing interests
All authors have completed the unified competing interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that Sanofi-Aventis provided a charitable donation to a primary care charity, but JAH, CJT, and FDRH and their institution (University of Birmingham) received no payment or support in kind for the work; FDRH has specified relationships that might have an interest in the submitted work in the previous 3 years: namely board membership of Pfizer Europe and Astra Zeneca Global, a consultancy for Takeda, Merck and Servier, grants from Roche diagnostics, he received payment for development of educational presentations from Astra Zeneca Global, Pfizer Europe, and Merck/Schering Plough, had travel/accommodation expenses covered by Boeringer Ingelheim, Astra Zeneca, Servier, and Pfizer, and sat on boards of PCCS, EPCCS, BCS; CJT was paid a speaker fee for a BMJ Masterclass, and has been paid travel and accommodation expenses by the Royal College of General Practitioners; JAH has declared no competing interests.

Acknowledgments
The authors did not have access to the original dataset. This report has been produced with reference to a study conducted, and a report produced, by the GPRD Group within the UK Medicines and Healthcare Products Regulatory Agency using the Full Feature General Practice Research Database. However, the interpretation and conclusions contained in this report are those of the authors alone.

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Beta-2 agonists
The RR of incident AF for current use of beta-2 agonists was found to be 1.30 (95% CI = 1.16 to 1.46). The RR for recent and past use remained significant, but considerably weakened. Conversely, the RR for current use of beta-2 agonists was 0.78 (95% CI = 0.70 to 0.88) when patients with an index date prior to 1996 were excluded, indicating a significant protective effect.

Statins
A protective effect of 18% was found for current use of statins, with a similar effect for past use, though the effect for recent use was not significant.

Other
No relationship was found between use of bisphosphonates, RAAS agents, or xanthine derivates and the risk of developing AF.

Relative risk by time elapsed
The association between AF and time since start of the disease or start of drug therapy was evaluated using Spline regression for COPD, CVA, diabetes, heart failure, hyperthyroidism, IHD, RAAS agents, bisphosphonates, oral glucocorticoids, statins, xanthine derivates, and beta-2 agonists. The AF risk in relation to the length of time since last prescription was also considered for each drug.

For each disease or treatment, the adjusted RR of developing AF was assessed for 8 years after diagnosis or from the start of therapy (and for the drugs the RR since last prescription). The time lapse appears to have no impact on the association between AF and COPD or diabetes. The risk of AF associated with heart failure or hyperthyroidism does not reduce over time. For CVA and IHD, the association is found only for the first 3 years after diagnosis. For the pharmacoepidemiological risk factors — notably RAAS agents, oral glucocorticoids, and statins — there appears to be some evidence of a different degree of effect approximately 3 years after the start of treatment, though this varies in both strength and direction.

DISCUSSION

Summary
Heart failure, IHD, hypertension, hyperthyroidism, heavy alcohol use, and obesity continue as significant risk factors associated with AF in this large UK primary care dataset based on contemporary and historical data. The risk of AF in patients with heart failure and hyperthyroidism does not reduce over time. It was found that diabetes and being a current smoker were not significant risk factors (though one should be wary of extrapolating from the results obtained that they have any protective effect). No association was found for COPD.

Oral glucocorticoids and beta-2 agonists may have a small adverse effect on AF onset, and statins may have a small protective effect that is sustained over a period of time. No significant effect was identified for RAAS agents, xanthine derivates, or bisphosphonates.

Strengths and limitations
Strengths of this study are that it used more up-to-date data than the previous analysis of associated factors with incident AF that utilised GPRD data,[21] and also considered additional factors the previous work did not. This analysis benefited from the generic strengths of GPRD, as previous validation studies have confirmed the validity and data completeness of the clinical data in it.[60] Due to the large number of cases included, the present study provides reliable risk estimates. It was also possible to examine time trends in the association between time since start of diagnosis or drug use and the risk of developing AF.

Limitations of the analysis are that comparison groups were not randomised; no information was available on all risk factors for stroke (such as frailty); onset of AF symptoms may not always be similar to the date of their first recording in the GPRD; and diagnoses of AF were not verified — the data quality markers for the GPRD do not include assessments of the accuracy of diagnoses or the appropriateness of Read terms selected. Although for this analysis no information was available on the diagnostic criteria used for AF diagnosis (such as electrocardiograms), a previous GPRD study reported a high level of validity in the recording of AF by GPs.[21] However, even beyond the issue of GPRD accuracy, clearly only cases diagnosed with AF could be considered in the model, and previous research has suggested that as many as 10% of AF cases may be undiagnosed in some populations.[61]

There are also some generic limitations of the GPRD dataset, including under-recording of some minor comorbidities used to identify patients with a contraindication for anticoagulation, missing data on smoking, BMI, and alcohol consumption, and a lag time before data are available.

Comparison with existing literature
The study identified similar medical risk

factors to previous research: high BMI, excessive alcohol consumption, prior cardiovascular morbidity, heart failure, IHD, and hyperthyroidism; but, like Ruigómez *et al*,[21] no effect of being a current smoker was shown. Perhaps more interestingly, the present findings provide further evidence that beta-2 agonists are a risk factor for developing AF and that statins offer some protection, while contradicting the literature that suggests glucocorticoids are protective; indeed, the current results suggest that glucocorticoids or the conditions they are treating are another risk factor for AF. Spline regression calculation showing a small continuing risk over time appears to confirm this. The study findings in fact mirror those of another large case–control study from Denmark,[29] which also found that current use of glucocorticoids but not past use was associated with increased risk of developing AF, to which it can now be added that recent use (3–12 months prior) is equally not associated with AF risk. The much larger sample of the present study supports the findings of previous GPRD-based research that biphosphonates[52] are not associated with AF risk, and xanthine derivates[56] (if at all) are only very weakly associated.

Rather than the significant protective effect that RAAS agents are reported to provide against AF in much of the literature, the present study found no such effect associated with their current use, thus contradicting even case–control studies,[36,37] although these focused specifically on hypertensive patients and compared the effects of ACEIs and ARBs to other antihypertensive drugs, namely diuretics or calcium-channel blockers. In this context, it is critical to recognise that the present non-randomised study may be vulnerable to unmeasured and uncontrolled confounding, especially by the diseases that lead to glucocorticoid or RAAS agent use.

Implications for practice

As the number of patients with AF is likely to increase without appropriate prevention strategies as the population ages, the importance of understanding the association of this condition with other clinical factors will likewise grow. In particular, a thorough understanding of the risks associated with the use of specific drugs will be essential in treating not only patients with existing AF, but also those whose treatment for other conditions may put them at risk for — or protect them from — developing AF.

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