The treatment of paroxysmal atrial fibrillation in UK primary care

Isaew, Andrea; Adderley, Nicola; Ryan, Ronan; Fitzmaurice, David; Marshall, Tom

DOI:
10.1136/heartjnl-2016-310927

Document Version
Peer reviewed version

Citation for published version (Harvard):
Isaew, A, Adderley, N, Ryan, R, Fitzmaurice, D & Marshall, T 2017, 'The treatment of paroxysmal atrial fibrillation in UK primary care', *Heart*, vol. 103, no. 19, pp. 1502-1507. https://doi.org/10.1136/heartjnl-2016-310927

Title

The treatment of paroxysmal atrial fibrillation in UK primary care.

Authorship

Andrea Isaew,[1] Nicola Adderley,[2] Ronan Ryan,[3] David Fitzmaurice,[4] Tom Marshall[5]

[1] Clinical Research Nurse, Institute of Applied Health Research, University of Birmingham, Edgbaston, Birmingham, B15 2TT. UK

[2] Corresponding author. Research Fellow, Institute of Applied Health Research, University of Birmingham, Edgbaston, Birmingham, B15 2TT. UK

[3] Research Fellow, Institute of Applied Health Research, University of Birmingham, Edgbaston, Birmingham, B15 2TT. UK

[4] Professor and Clinical Lead for Primary Care Clinical Sciences, Institute of Applied Health Research, University of Birmingham, Edgbaston, Birmingham, B15 2TT. UK

[5] Professor of Public Health and Primary Care, Institute of Applied Health Research, University of Birmingham, Edgbaston, Birmingham, B15 2TT. UK

Correspondence

Correspondence should be addressed to Nicola Adderley. Email: n.j.adderley@bham.ac.uk

Telephone: +44 (0)121 414 5643

Statistics

Word count (abstract):	290
Word count (main text):	2160
Tables:	2 (+1 supplementary)
Figures:	1
References:	33

ABSTRACT

Objective

To determine whether patients with paroxysmal atrial fibrillation (AF) are less likely to be treated with anticoagulants than patients with persistent/permanent AF, and to investigate trends in treatment between 2000 and 2015. UK and European guidelines recommend that anticoagulants are offered to all AF patients at increased risk of stroke, irrespective of AF type.

Methods

16 sequential cross-sectional analyses from 2000 to 2015 were carried out with index dates on 1st May each year. The data source was primary care data from 648 practices across the UK contributing to The Health Improvement Network (THIN) database. All patients with a diagnosis of AF aged ≥ 35 years and registered for at least one year were included. The main outcome measure was prescription of anticoagulant medication.

Results

The proportion of AF patients with a diagnosis of paroxysmal AF increased from 7.4% (95% CI 7.0, 7.8) in 2000 to 14.0% (95% CI 13.7, 14.3) in 2015. Among patients with a $CHADS_2$ score ≥ 1, between 2000 and 2015 the proportion prescribed anticoagulants increased from 18.8% (95% CI 16.4, 21.4) to 56.2% (95% CI 55.0, 57.3) and from 34.2% (95% CI 33.3, 35.0) to 69.4% (95% CI 68.9, 69.8) in paroxysmal and other (persistent/permanent) AF patients respectively; RR for treatment of paroxysmal AF patients compared to other AF patients increased from 0.48 (95% CI 0.42, 0.55) to 0.76 (95% CI 0.74, 0.77). Adjusting for age, sex, Townsend score and presence or absence of contraindications had little effect on the results.

Conclusions

In 2000, eligible paroxysmal AF patients were half as likely to be treated with anticoagulants as other AF patients; this has improved over time, but in 2015, eligible paroxysmal AF patients were still around 20% less likely to be prescribed anticoagulant medication.

KEY MESSAGES

What is already known about this subject?

Patients with paroxysmal atrial fibrillation (AF) are at an elevated risk of stroke. Guidelines recommend anticoagulants for patients with paroxysmal AF**.**

What does this study add?

In 2000 patients with paroxysmal AF were half as likely to be prescribed anticoagulants as those with permanent AF. In 2015 patients with paroxysmal AF were 20% less likely to be prescribed anticoagulants as those with permanent AF.

How might this impact on clinical practice?

Clinicians should be aware that eligible patients with paroxysmal AF should be prescribed anticoagulants.

THE TREATMENT OF PAROXYSMAL ATRIAL FIBRILLATION IN UK PRIMARY CARE

INTRODUCTION

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and a major global public health problem. It is associated with a five-fold increase in risk of stroke, increased incidence of congestive heart failure, and higher mortality.[1]

Recurrent AF is either labelled 'paroxysmal' when it is self-terminating or 'persistent' when it lasts more than 7 days or is terminated earlier using either pharmacological means or direct current cardioversion; AF is defined as permanent when cardioversion fails to restore normal heart rhythm.[2] Evidence varies regarding the similarity in stroke risk between paroxysmal, persistent and permanent AF patients: some studies have shown comparable stroke risk, while others suggest that risk may be lower in paroxysmal AF patients.[3,4,5,6,7,8] Nevertheless, paroxysmal AF patients remain at an elevated risk of stroke relative to patients without AF. Within 1.5 years over a fifth of patients with paroxysmal AF progress to permanent AF.[9,10]

Prophylactic treatment of AF with anticoagulants reduces risk of stroke by approximately two thirds.[11,12,13,14,15] Current UK and European guidelines recommend that anticoagulants are offered to all AF patients with a CHA_2DS_2-VASc score ≥ 2, and are considered for men with a CHA_2DS_2-VASc score of 1, regardless of whether the pattern of AF is paroxysmal, persistent or permanent, or the duration of AF.[1,16,17,18]

Recent data from two international studies, the GARFIELD Registry and the GLORIA-AF Registry, indicate that anticoagulant therapy is not consistently prescribed across AF categories, with lower rates of use in paroxysmal AF patients than in those with persistent or permanent AF.[19,20,21]

The aim of this analysis was to determine whether patients with paroxysmal AF are less likely to be treated with anticoagulants than patients with persistent or permanent AF in the UK, and to investigate trends in treatment between 2000 and 2015. To date, this question has not been addressed in a UK primary care setting.

METHODS

Data source

Analysis was performed using data from The Health Improvement Network (THIN), an anonymised database of electronic medical records from UK general practices using Vision software. The version of the THIN database used in this study (THIN1505) included primary care data for approximately 14.0 million patients at 648 practices across the UK. General practices were eligible for inclusion in the study from the latest of: the practice acceptable mortality recording (AMR) date,[22] the Vision installation date, and the study start date (one year prior to the first index date).

Study design

Sixteen sequential cross-sectional analyses were carried out with index dates on 1st May each year from 2000 to 2015. All analyses were conducted using StataIC 13. Data was not used prior to 2000 as there were fewer practices and patients contributing data, and data accuracy is better in more recent years.

The study population included all patients with a diagnosis of atrial fibrillation aged 35 years and over on the index date who were registered at least one year prior to the index date. The exposure was a diagnosis of paroxysmal AF, with all other types of AF (persistent or permanent AF, hereafter referred to as 'other AF') as the comparator group. Outcome was treatment with anticoagulants.

Analysis

The proportions of patients with paroxysmal AF and other AF prescribed anticoagulants on each index date were calculated, with 95% confidence intervals (CI); p-values for trends in treatment between 2000 and 2015 were calculated using chi-squared tests. Patients were stratified according to eligibility for anticoagulant treatment: in primary analysis, this was defined according to $CHADS_2$ score (≥ 1), since $CHADS_2$ score has been in use for a longer period of time than CHA_2DS_2-VASc score;[23,24] in sensitivity analysis, eligibility was defined according to CHA_2DS_2-VASc score (≥ 1). Crude and adjusted risk ratios (RR) were calculated on each index date. RRs were calculated using Cox regression, setting follow-up time to 1 for all patients, using the Breslow method to break ties, and using the robust variance estimator;[25] RRs were adjusted for age and sex only, and for age, sex, Townsend score, $CHADS_2$ score, and presence of any contraindication.

Definitions of variables

AF was defined as a clinical code for atrial fibrillation or atrial flutter recorded ever prior to the index date, excluding patients with a clinical code indicating AF resolved recorded on or after the last recorded AF clinical code and prior to the index date. Patients were categorised as having paroxysmal AF if the last AF clinical code prior to the index date indicated paroxysmal atrial fibrillation or paroxysmal atrial flutter; otherwise patients were categorised as having other (persistent or permanent) AF. Current anticoagulant treatment was defined as a record of a prescription for any anticoagulant drug (including warfarin, parenteral anticoagulants, other vitamin K antagonists and new oral anticoagulants) within 90 days prior to the index date or a clinical code indicating provision of anticoagulant therapy within 365 days prior to the index date.

$CHADS_2$ scores were calculated by adding one point for a history of congestive heart failure, hypertension, age ≥ 75 and diabetes, and two points for a history of stroke or transient ischaemic attack (TIA). CHA_2DS_2-VASc scores were calculated by adding one point for a history of congestive heart failure, hypertension, diabetes, vascular disease, age 65-74 years and female sex (if another risk factor was present, otherwise 0), and two points for age ≥ 75 and history of stroke, TIA or thromboembolism. History of congestive heart failure, stroke, TIA, thromboembolism, vascular disease and diabetes were defined by a relevant clinical code recorded ever prior to the index date, excluding patients with a clinical code indicating diabetes resolved recorded after the last recorded diabetes code and prior to the index date; hypertension was defined as a current (previous 90 days) prescription of antihypertensive drugs or the mean of the three most recent systolic blood pressures in the last 3 years ≥160 mm Hg.

Contraindications to anticoagulants were defined as a clinical code within the 2 years prior to the index date of peptic ulcer, intracranial, intraocular or retroperitoneal bleeding, bleeding disorders, haemorrhagic stroke, oesophageal varices, aneurysm, or proliferative retinopathy; a clinical code recording allergy or adverse reactions to anticoagulants ever prior to the index date; a clinical code indicating pregnancy in the 9 months prior to the index date; or severe hypertension with a mean (of the 3 most recent measures in the last 3 years prior to the index date) systolic blood pressure >200 mm Hg or diastolic blood pressure >120 mm Hg.

RESULTS

A total of 179,343 of the 4,419,659 patients eligible for inclusion in the study between 2000 and 2015 had AF. As an individual could contribute to the analysis in more than one year, the analyses consisted of a total of 848,852 AF patient records. The proportion of AF patients with a diagnosis of paroxysmal AF increased from 7.4% (95% CI 7.0, 7.8) in 2000 to 14.0%

(95% CI 13.7, 14.3) in 2015, an increase in prevalence from 0.14% (95% CI 0.13, 0.15) to 0.43% (95% CI 0.42, 0.44). Baseline characteristics of paroxysmal and other (persistent/permanent) AF patients are shown in Table 1. Across all years, in paroxysmal compared to other AF patients the mean age was 4.5 years (95% CI 4.4, 4.6) lower; 6.4% (95% CI 6.1, 6.7) fewer were males; mean $CHADS_2$ score was 0.43 (95% CI 0.42, 0.44) points lower; 1.6% (95% CI 1.4, 1.8) fewer were in the most deprived Townsend quintile; and 0.5% (95% CI 0.4, 0.7) fewer had one or more contraindications to anticoagulants.

Over the 15 year period studied, the proportion of paroxysmal AF patients prescribed anticoagulants increased from 16.0% (95% CI 14.0, 18.2) to 50.7% (95% CI 49.6, 51.8), while the proportion of other AF patients prescribed anticoagulants increased from 33.5% (95% CI 32.7, 34.3) to 67.1% (95% CI 66.6, 67.5). Among eligible patients only, defined as those with a $CHADS_2$ score of 1 or more, the proportion of paroxysmal AF patients prescribed anticoagulants increased from 18.8% (95% CI 16.4, 21.4) to 56.2% (95% CI 55.0, 57.3), and the proportion of other AF patients increased from 34.2% (95% CI 33.3, 35.0) to 69.4% (95% CI 68.9, 69.8) (Figure 1).

In 2000, paroxysmal AF patients were half as likely to receive anticoagulant treatment as other AF patients, risk ratio (RR) 0.48 (95% CI 0.42, 0.55); this disparity has declined, particularly since 2011/12, but in 2015, paroxysmal AF patients are still less likely to be prescribed anticoagulants, RR 0.76 (95% CI 0.74, 0.77) (Table 2). Adjusting for age, sex, Townsend score, $CHADS_2$ score and presence or absence of contraindications made only a small difference to the results: fully adjusted RR increased from 0.41 (95% CI 0.36, 0.48) in 2000 to 0.77 (95% CI 0.75, 0.79) in 2015.

Among only those AF patients eligible for anticoagulant treatment, RR increased from 0.55 (95% CI 0.48, 0.63) to 0.81 (95% CI 0.79, 0.83) between 2000 and 2015. Adjusting for age,

sex, Townsend score and presence or absence of contraindications had little effect on the results in recent years, but caused an increase in effect size in earlier years: adjusted RR increased from 0.46 (95% CI 0.40, 0.53) in 2000 to 0.80 (95% CI 0.79, 0.82) in 2015 (Table 2); the slightly increased effect of adjustment in earlier years is likely to be due the greater difference in mean age between paroxysmal and other AF patients, particularly between 2000 and 2006. In sensitivity analysis, eligibility for anticoagulant treatment was defined according to CHA_2DS_2-VASc score (1 or more); this made only a marginal difference to the observed RRs (Supplementary Table 1).

Table 1: Baseline characteristic of AF patients with paroxysmal or other AF, 2000-2015

Year	AF type	n (%)	Age	Sex (male)	$CHADS_2$ score			Most deprived quintile	One or more contra-indication
					0	1	2+		
			Mean (SD)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
2000	Paroxysmal	1169 (7.4)	69.4 (12.5)	589 (50.4)	248 (21.2)	448 (38.3)	473 (40.5)	145 (13.1)	62 (5.3)
	Other	14627 (92.6)	75.5 (10.7)	7567 (51.7)	1613 (11.0)	3982 (27.2)	9032 (61.8)	1906 (14.0)	771 (5.3)
2001	Paroxysmal	2111 (8.6)	70.5 (12.4)	1027 (48.7)	422 (20.0)	759 (36.0)	930 (44.1)	226 (11.2)	117 (5.5)
	Other	22426 (91.4)	75.6 (10.8)	11740 (52.4)	2296 (10.2)	6018 (26.8)	14112 (62.9)	2731 (12.9)	1298 (5.8)
2002	Paroxysmal	2980 (9.4)	70.4 (12.3)	1467 (49.2)	574 (19.3)	1051 (35.3)	1355 (45.5)	316 (11.1)	183 (6.1)
	Other	28713 (90.6)	75.8 (10.7)	15101 (52.6)	2707 (9.4)	7439 (25.9)	18567 (64.7)	3492 (12.8)	1843 (6.4)
2003	Paroxysmal	4126 (10.1)	70.7 (12.2)	2023 (49.0)	762 (18.5)	1409 (34.2)	1955 (47.4)	441 (11.2)	270 (6.5)
	Other	36762 (89.9)	75.8 (10.8)	19510 (53.1)	3235 (8.8)	9469 (25.8)	24058 (65.4)	4355 (12.5)	2326 (6.3)
2004	Paroxysmal	4827 (10.6)	70.9 (12.2)	2333 (48.3)	789 (16.4)	1645 (34.1)	2393 (49.6)	519 (11.1)	313 (6.5)
	Other	40502 (89.4)	76.0 (10.8)	21533 (53.2)	3298 (8.1)	10162 (25.1)	27042 (66.8)	4716 (12.1)	2658 (6.6)
2005	Paroxysmal	5588 (10.9)	71.1 (12.3)	2705 (48.4)	905 (16.2)	1873 (33.5)	2810 (50.3)	568 (10.4)	336 (6.0)
	Other	45584 (89.1)	76.1 (10.8)	24411 (53.6)	3460 (7.6)	11478 (25.2)	30646 (67.2)	5209 (11.8)	2944 (6.5)
2006	Paroxysmal	6476 (11.6)	71.4 (12.2)	3127 (48.3)	1022 (15.8)	2162 (33.4)	3292 (50.8)	661 (10.5)	350 (5.4)
	Other	49463 (88.4)	76.2 (10.9)	26666 (53.9)	3586 (7.3)	12301 (24.9)	33576 (67.9)	5645 (11.8)	3152 (6.4)
2007	Paroxysmal	6781 (11.6)	72.0 (12.1)	3269 (48.2)	923 (13.6)	2242 (33.1)	3616 (53.3)	658 (10.0)	371 (5.5)
	Other	51714 (88.4)	76.6 (10.7)	28036 (54.2)	3224 (6.2)	12689 (24.5)	35801 (69.2)	5739 (11.4)	3116 (6.0)
2008	Paroxysmal	7460 (12.1)	72.3 (12.0)	3556 (47.7)	960 (12.9)	2453 (32.9)	4047 (54.3)	715 (9.8)	372 (5.0)
	Other	54066 (87.9)	76.8 (10.7)	29567 (54.7)	3099 (5.7)	12938 (23.9)	38029 (70.3)	6048 (11.5)	3238 (6.0)
2009	Paroxysmal	8299 (12.7)	72.4 (11.9)	3981 (48.0)	1029 (12.4)	2733 (32.9)	4537 (54.7)	794 (9.8)	437 (5.3)
	Other	57253 (87.3)	76.8 (10.6)	31659 (55.3)	3019 (5.3)	13554 (23.7)	40680 (71.1)	6288 (11.2)	3532 (6.2)
2010	Paroxysmal	8620 (13.0)	72.4 (12.1)	4175 (48.4)	1065 (12.4)	2818 (32.7)	4737 (55.0)	830 (9.9)	463 (5.4)
	Other	57825 (87.0)	76.9 (10.7)	32263 (55.8)	2899 (5.0)	13567 (23.5)	41359 (71.5)	6316 (11.2)	3561 (6.2)
2011	Paroxysmal	9182 (13.5)	72.6 (12.0)	4413 (48.1)	1090 (11.9)	2982 (32.5)	5110 (55.7)	863 (9.6)	516 (5.6)
	Other	59011 (86.5)	77.0 (10.7)	33171 (56.2)	2891 (4.9)	13689 (23.2)	42431 (71.9)	6356 (11.0)	3587 (6.1)
2012	Paroxysmal	9641 (13.8)	72.7 (12.0)	4650 (48.2)	1138 (11.8)	3065 (31.8)	5438 (56.4)	875 (9.3)	514 (5.3)
	Other	60012 (86.2)	77.0 (10.7)	33900 (56.5)	2899 (4.8)	13834 (23.1)	43279 (72.1)	6508 (11.1)	3734 (6.2)
2013	Paroxysmal	9638 (13.9)	72.7 (12.0)	4754 (49.3)	1156 (12.0)	3015 (31.3)	5467 (56.7)	890 (9.5)	551 (5.7)
	Other	59595 (86.1)	76.9 (10.8)	33956 (57.0)	2984 (5.0)	13677 (23.0)	42934 (72.0)	6618 (11.4)	3697 (6.2)
2014	Paroxysmal	9368 (14.0)	72.7 (12.1)	4674 (49.9)	1136 (12.1)	2919 (31.2)	5313 (56.7)	860 (9.4)	568 (6.1)
	Other	57580 (86.0)	76.9 (10.8)	32939 (57.2)	2913 (5.1)	13028 (22.6)	41639 (72.3)	6206 (11.0)	3525 (6.1)
2015	Paroxysmal	8036 (14.0)	72.7 (12.2)	4082 (50.8)	1006 (12.5)	2458 (30.6)	4572 (56.9)	753 (9.6)	467 (5.8)
	Other	49417 (86.0)	76.9 (10.9)	28534 (57.7)	2544 (5.2)	11172 (22.6)	35701 (72.2)	5428 (11.3)	2886 (5.8)

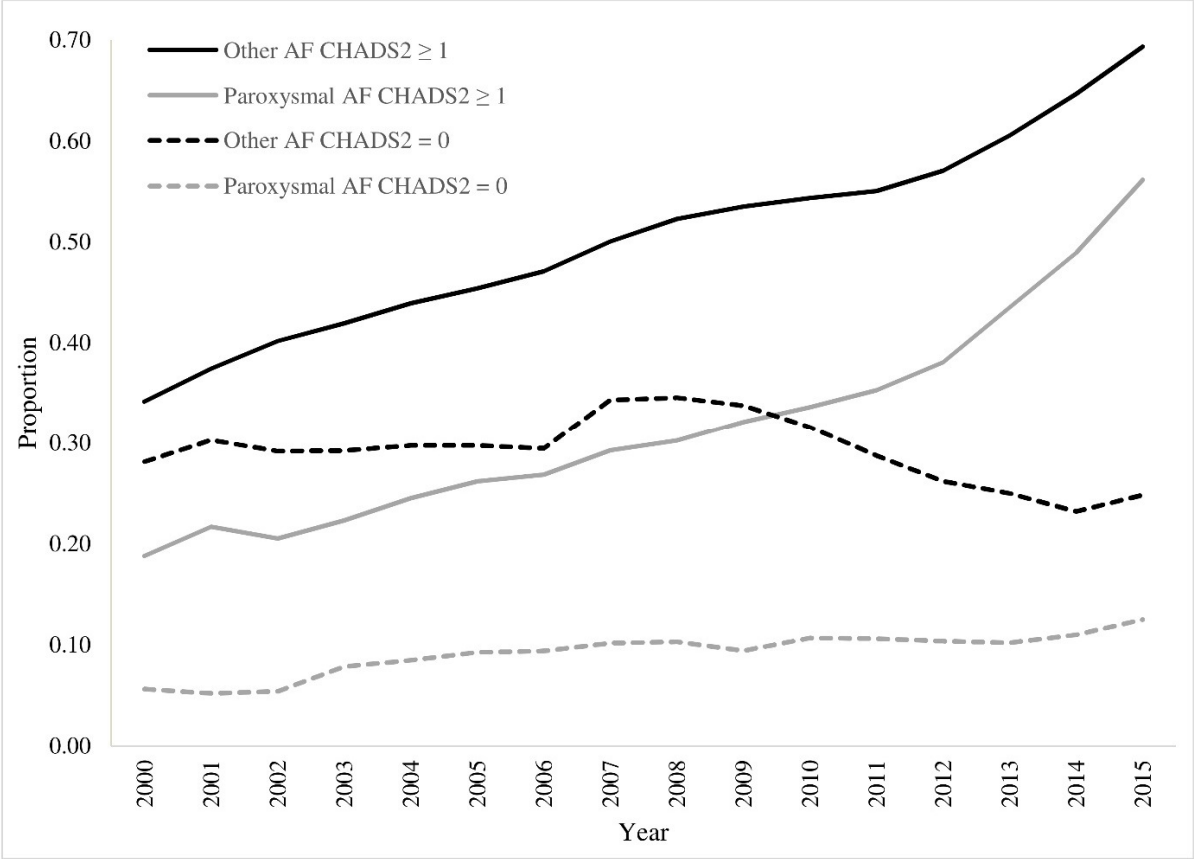

Figure 1. Proportion of paroxysmal and other AF patients prescribed anticoagulant treatment by $CHADS_2$ score, 2000-2015

Table 2: Risk ratios for anticoagulant treatment of paroxysmal AF patients relative to other AF patients, 2000-2015

Year	All			Eligible $CHADS_2 \geq 1$		Ineligible $CHADS_2 = 0$
	Unadjusted	Adjusted for age and sex	Fully adjusted[†]	Unadjusted	Fully adjusted[††]	Unadjusted
	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)
2000	0.48 (0.42, 0.55)	0.43 (0.37, 0.49)	0.41 (0.36, 0.48)	0.55 (0.48, 0.63)	0.46 (0.40, 0.53)	0.20 (0.12, 0.34)
2001	0.50 (0.46, 0.55)	0.46 (0.42, 0.51)	0.46 (0.42, 0.51)	0.58 (0.53, 0.64)	0.52 (0.48, 0.58)	0.17 (0.11, 0.26)
2002	0.45 (0.42, 0.49)	0.42 (0.39, 0.46)	0.42 (0.38, 0.45)	0.51 (0.47, 0.55)	0.47 (0.43, 0.51)	0.19 (0.13, 0.26)
2003	0.48 (0.45, 0.51)	0.46 (0.43, 0.49)	0.46 (0.43, 0.49)	0.53 (0.50, 0.57)	0.50 (0.47, 0.53)	0.27 (0.21, 0.35)
2004	0.51 (0.49, 0.54)	0.49 (0.46, 0.52)	0.49 (0.46, 0.52)	0.56 (0.53, 0.59)	0.52 (0.49, 0.55)	0.29 (0.23, 0.36)
2005	0.53 (0.51, 0.56)	0.51 (0.49, 0.54)	0.51 (0.48, 0.53)	0.58 (0.55, 0.61)	0.54 (0.51, 0.57)	0.31 (0.25, 0.39)
2006	0.53 (0.50, 0.55)	0.51 (0.49, 0.53)	0.51 (0.48, 0.53)	0.57 (0.55, 0.60)	0.54 (0.51, 0.56)	0.32 (0.26, 0.39)
2007	0.54 (0.52, 0.57)	0.52 (0.50, 0.55)	0.52 (0.50, 0.54)	0.58 (0.56, 0.61)	0.55 (0.53, 0.58)	0.30 (0.24, 0.36)
2008	0.54 (0.52, 0.56)	0.52 (0.50, 0.54)	0.52 (0.50, 0.54)	0.58 (0.56, 0.60)	0.55 (0.53, 0.57)	0.30 (0.25, 0.36)
2009	0.56 (0.54, 0.58)	0.55 (0.53, 0.57)	0.55 (0.53, 0.56)	0.60 (0.58, 0.62)	0.58 (0.56, 0.60)	0.28 (0.23, 0.34)
2010	0.58 (0.56, 0.60)	0.57 (0.55, 0.59)	0.57 (0.55, 0.59)	0.62 (0.60, 0.64)	0.60 (0.58, 0.62)	0.34 (0.28, 0.41)
2011	0.60 (0.58, 0.62)	0.60 (0.58, 0.62)	0.60 (0.58, 0.62)	0.64 (0.62, 0.66)	0.63 (0.61, 0.65)	0.37 (0.31, 0.44)
2012	0.63 (0.61, 0.64)	0.63 (0.61, 0.65)	0.63 (0.61, 0.64)	0.67 (0.65, 0.69)	0.65 (0.64, 0.67)	0.40 (0.33, 0.47)
2013	0.67 (0.66, 0.69)	0.68 (0.66, 0.70)	0.68 (0.66, 0.70)	0.72 (0.70, 0.74)	0.71 (0.69, 0.73)	0.41 (0.34, 0.49)
2014	0.71 (0.69, 0.73)	0.72 (0.71, 0.74)	0.72 (0.70, 0.74)	0.76 (0.74, 0.77)	0.75 (0.73, 0.77)	0.47 (0.40, 0.57)
2015	0.76 (0.74, 0.77)	0.77 (0.76, 0.79)	0.77 (0.75, 0.79)	0.81 (0.79, 0.83)	0.80 (0.79, 0.82)	0.50 (0.42, 0.60)

All p values < 0.001. [†]Adjusted for age, sex, Townsend score, $CHADS_2$ score and presence or absence of contraindications (binary). [††]Adjusted for age, sex, Townsend score and presence or absence of contraindications.

DISCUSSION

Paroxysmal AF is becoming more commonly recorded as a diagnosis in UK primary care. Patients with paroxysmal AF are less likely to be treated with anticoagulants than patients with other types of AF: in 2000, paroxysmal AF patients who were eligible for treatment were almost half as likely to receive anticoagulants as other AF patients, and while this has been steadily improving over the last 15 years, paroxysmal AF patients continue to be around 20% less likely to receive anticoagulants than other AF patients. This holds true after adjusting the data for age, sex and other potential confounders. The absolute anticoagulant treatment gap for paroxysmal AF remained relatively constant between 2002 and 2012, at around 20%; in recent years, this gap has narrowed, but remains around 13%.

These results are consistent with findings from studies carried out in the USA among hospital outpatients with AF, in which paroxysmal AF patients were found to be around 20% less likely to receive oral anticoagulants than patients with persistent/permanent AF after adjusting for potential confounders.[26,27] Similar results were also found in a study of AF patients admitted to hospital in Greece,[28] and in the Euro Heart Survey on Atrial Fibrillation, an observational study of AF patients attending hospital in the ESC member countries (including the UK).[29] No comparable studies using primary care data in the UK are known to the authors.

ESC guideline-adherent antithrombotic management is associated with significantly better outcomes, including those related to mortality, thromboembolism, stroke and transient ischaemic attack.[30] Current treatment practice does not appear to closely follow published treatment guidelines,[31] which most likely results in elevated levels of preventable ischaemic stroke among patients with paroxysmal AF, even more so than in the wider atrial fibrillation population, leading to greater morbidity, mortality and overall cost to health care systems.[32,33]

Further research is needed to establish whether the difference in treatment between paroxysmal and other AF patients is the result of lower levels of treatment initiation by clinicians or whether paroxysmal AF patients are more likely to stop their treatment, and to explore reasons why this is the case.[20] This will facilitate the development of methods to improve guideline adherence and/or uptake of anticoagulant prophylaxis, leading to improved outcomes for patients with paroxysmal AF.[7]

Strengths and limitations

This study utilises a large dataset which is representative of the AF population in UK primary care, and includes recent data up to 2015. The dataset comprises routinely collected data used by GPs to make clinical decisions.

It is possible that AF type could be misclassified, as some cases of paroxysmal AF may be recorded under a non-specific AF clinical code; however, this is more likely to dilute rather than inflate observed effect sizes. Treatment may be underreported if patients are prescribed anticoagulants by their hospital; however, most anticoagulants are prescribed in primary care, and most secondary care prescriptions should be captured by anticoagulant/INR monitoring clinical codes, so underreporting is likely to be minimal.

CONCLUSION

Patients with paroxysmal AF are less likely to be treated with anticoagulants than patients with persistent or permanent AF. This difference is not explained by differences in patient demographics, stroke risk, or contraindications. The question remains as to whether the difference in treatment between paroxysmal and other AF patients is the result of lower levels of treatment initiation by clinicians or whether paroxysmal AF patients are more likely to stop their treatment, and to explore the reasons why.

CONTRIBUTION

AI had the original research idea. RR undertook data extraction. NA designed and performed the analysis. NA and AI wrote the first draft of the paper, which was revised in collaboration with TM, DF and RR.

FUNDING

Nicola Adderley and Tom Marshall are funded by the NIHR CLAHRC West Midlands initiative. This paper presents independent research and the views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

COMPETING INTERESTS

The authors have no competing interests to declare.

ETHICS

The THIN data collection scheme and research carried out using THIN data were approved by the NHS South-East Multicentre Research Ethics Committee (MREC) in 2003; under the terms of this ethics approval, studies must undergo scientific review. Approval for this analysis was obtained from the Scientific Review Committee (for the use of THIN data) on 2nd April 2015 (SRC reference number 15THIN021).

LICENCE

permit this article (if accepted) to be published in HEART editions and any other BMJPGL products to exploit all subsidiary rights.

TRANSPARENCY DECLARATION

The lead author, Andrea Isaew, affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

[1] Camm AJ, Lip GYH, De Caterina R, et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation. An update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. *Eur Heart J* 2012; 33(21): 2719-47. doi: 10.1093/eurheartj/ehs253

[2] Fuster V, Rydén LE, Cannom DS, et al. American College of Cardiology Foundation/American Heart Association Task Force 2011 ACCF/AHA/HRS focused updates incorporated into the ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation* 2011;123(10): e269–e367.

[3] Hart RG, Pearce LA, Rothbart RM, et al. for the Stroke Prevention in Atrial Fibrillation Investigators. Stroke with intermittent atrial fibrillation: incidence and predictors during aspirin therapy. *J Am Coll Cardiol* 2000;35(1):183–187.

[4] Steinberg BA, Hellkamp AS, Lokhnygina Y, et al. ROCKET-AF Steering Committee and Investigators. Higher risk of death and stroke in patients with persistent vs. paroxysmal atrial fibrillation: results from the ROCKET-AF Trial. *Eur Heart J* 2015;36(5):288-96.

[5] Chiang CE, Naditch-Brûlé L, MurinJ, et al. Distribution and Risk Profile of Paroxysmal, Persistent, and Permanent Atrial Fibrillation in Routine Clinical Practice. Insight From the Real-Life Global Survey Evaluating Patients With Atrial Fibrillation International Registry *Circ Arrhythm Electrophysiol* 2012;5: 632-639.

[6] Vanassche T, Lauw MN, Eikelboom JW, et al. Risk of ischaemic stroke according to pattern of atrial fibrillation: analysis of 6563 aspirin-treated patients in ACTIVE-A and AVERROES. *Eur Heart J* 2015;36(5):281-7a.

[7] Aronis KN, Thigpen JL, Tripodis Y, et al. Paroxysmal atrial fibrillation and the hazards of under-treatment. *Int J Cardiol* 2016;202:214-20. doi: 10.1016/j.ijcard.2015.09.006

[8] Lip GYH, Frison L, Grind M, On behalf of the SPORTIF Investigators. Stroke event rates in anticoagulated patients with paroxysmal atrial fibrillation. *Journal of Internal Medicine* 2008;264:50-61. doi: 10.1111/j.1365-2796.2007.01909.x

[9] Ruigómez A, Johansson S, Wallander MA, et al. Predictors and prognosis of paroxysmal atrial fibrillation in general practice in the UK. BMC Cardiovascular Disorders. 2005;5:20. doi: 10.1186/1471-2261-5-20

[10] Holmqvist F, Kim S, Steinberg BA, et al. on behalf of the ORBIT-AF Investigators. Heart rate is associated with progression of atrial fibrillation, independent of rhythm. *Heart* 2015;101:11 894-899 Published OnlineFirst*:* 2 March 2015 doi:10.1136/heartjnl-2014-307043

[11] Aguilar MI, Hart R. Oral anticoagulants for preventing stroke in patients with non-valvular atrial fibrillation and no previous history of stroke or transient ischemic attacks. Cochrane Database of Systematic Reviews 2005, Issue 3. Art. No.: CD001927. doi: 10.1002/14651858.CD001927.pub2

[12] Aguilar MI, Hart R, Pearce LA. Oral anticoagulants versus antiplatelet therapy for preventing stroke in patients with non-valvular atrial fibrillation and no history of stroke or transient ischemic attacks. Cochrane Database of Systematic Reviews 2007, Issue 3. Art. No.: CD006186. doi: 10.1002/14651858.CD006186.pub2

[13] Connolly SJ, Ezekowitz MD, Yusuf S, et al. the RE-LY Steering Committee and Investigators. Dabigatran versus Warfarin in Patients with Atrial Fibrillation. *N Engl J Med* 2009;361(12):1139-1151. doi: 10.1056/NEJMoa0905561

[14] Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 201;365:981–992.

[15] Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011;365:883– 891.

[16] National Clinical Guideline Centre. Atrial fibrillation: the management of atrial fibrillation. Clinical guideline: Methods, evidence and recommendations. London: National Institute for Health and Care Excellence (UK) 2014.

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

[18] January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation, A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. 2014 AHA/ACC/HRS Atrial Fibrillation Guideline

[19] Lip GYH, Rushton-Smith SK, Goto S, Verheugt FWA, Goldhaber SZ, Haas S, Bassand JP, Mueller I, Kakkar AK, for the GARFIELD Investigators. Patterns of antithrombotic therapy and type of atrial fibrillation: insights from the Global Anticoagulant Registry in the FIELD (GARFIELD). Eur Heart J 2012;33(suppl 1):54. P562. Available at: http://eurheartj.oxfordjournals.org/content/ehj/33/suppl_1/19.full.pdf [Last accessed 17th January 2017]

[20] Kakkar AK, Mueller I, Bassand JP, et al. Risk profiles and antithrombotic treatment of patients newly diagnosed with atrial fibrillation at risk of stroke: perspectives from the from the international, observational, prospective. GARFIELD registry, *PLOS One* 8, e63479 (2013).

[21] Huisman MV, Rothman KJ, Paquette M, Teutsch C, Diener HC, Dubner SJ, Halperin JL, Ma C, Zint K, Elsaesser A, Bartels DB, Lip GY; GLORIA-AF Investigators. Antithrombotic Treatment Patterns in Patients with Newly Diagnosed Nonvalvular Atrial Fibrillation: The GLORIA-AF Registry, Phase II. Am J Med. 2015 Dec;128(12):1306-13.e1. doi: 10.1016/j.amjmed.2015.07.013

[22] Maguire A, Blak BT, Thompson M. The importance of defining periods of complete mortality reporting for research using automated data from primary care. *Pharmacoepidemiology and Drug Safety* 2009;18:76-83.

[23] Gage BF, Waterman AD, Shannon W, et al. Validation of Clinical Classification Schemes for Predicting Stroke. Results From the National Registry of Atrial Fibrillation. *JAMA* 2001;285:2864-2870. doi:10.1001/jama.285.22.2864

[24] Lip GY, Nieuwlaat R, Pisters R, et al. Refining Clinical Risk Stratification for Predicting Stroke and Thromboembolism in Atrial Fibrillation Using a Novel Risk Factor-Based Approach: The Euro Heart Survey on Atrial Fibrillation. *Chest* 2010;137:263-72. doi: 10.1378/chest.09-1584

[25] Cummings P. Methods for estimating adjusted risk ratios. *The Stata Journal* 2009;9:176-196.

[26] Hsu JC; Chan PS; Tang F; Maddox TM; Marcus GM. Differences in Anticoagulant Therapy Prescription in Patients with Paroxysmal Versus Persistent Atrial Fibrillation. *Am J Med* 2015; 128(6): 654.e1-654.e10.

[27] Waldo AL, Becker RC, Tapson VF, et al. Hospitalized patients with atrial fibrillation and a high risk of stroke are not being provided with adequate anticoagulation. *J Am Coll Cardiol* 2005;46:1729–1736.

[28] Pipilis A, Farmakis D, Kaliambakos S, et al. on behalf of the RAFTING Investigators. Anticoagulant therapy is prescribed less often in paroxysmal atrial fibrillation regardless of thromboembolic risk: Results from the Registry of Atrial Fibrillation To Investigate New Guidelines (RAFTING). *Int J Cardiol* 2014;175:569-70. doi: 10.1016/j.ijcard.2014.05.032

[29] Nieuwlaat R, Capucci A, Camm AJ, et al. on behalf of the Euro Heart Survey Investigators. Atrial fibrillation management: a prospective survey in ESC Member Countries. The Euro Heart Survey on Atrial Fibrillation. *Eur Heart J* 2005;26:2422–2434. doi: 10.1093/eurheartj/ehi505

[30] Lip GYH, Laroche C, Popescu MI, et al. Improved outcomes with European Society of Cardiology guideline-adherent antithrombotic treatment in high-risk patients with atrial fibrillation: a report from the EORP-AF General Pilot Registry. *Europace* 2015;17:1777–1786. doi: 10.1093/europace/euv269.

[31] Atrial Fibrillation Association and Anticoagulation Europe (UK). The AF Report. Atrial Fibrillation: Preventing a Stroke Crisis. 2011. Available at www.afa.org.uk and www.anticoagulationeurope.org [Last accessed 18th October 2016]

[32] Ogilvie IM, Newton N, Welner SA, et al. Underuse of Oral Anticoagulants in Atrial Fibrillation: A Systematic Review. *Am J Med* 2010;123(7): 638-645.e4. doi: 10.1016/j.amjmed.2009.11.025.

[33] Camm AJ, Kirchhof P, Lip GY, et al. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). 8/22/14. *Eur Heart J* 2010;31(19):2369-429.6/16/15. doi: 10.1093/eurheartj/ehq278

Supplementary Table 1: Risk ratios for treatment of paroxysmal AF patients relative to other AF patients using CHA_2DS_2-VASc score to define eligibility, 2000-2015

Year	Eligible CHA_2DS_2-VASc ≥ 1		Ineligible CHA_2DS_2-VASc = 0
	Unadjusted	Fully adjusted[†]	Unadjusted
	RR (95% CI)	RR (95% CI)	RR (95% CI)
2000	0.52 (0.46, 0.60)	0.44 (0.38, 0.51)	0.17 (0.08, 0.38)
2001	0.55 (0.50, 0.60)	0.50 (0.45, 0.55)	0.16 (0.09, 0.30)
2002	0.50 (0.46, 0.54)	0.45 (0.42, 0.49)	0.12 (0.06, 0.22)
2003	0.52 (0.49, 0.55)	0.49 (0.45, 0.52)	0.27 (0.19, 0.40)
2004	0.55 (0.52, 0.58)	0.52 (0.49, 0.54)	0.19 (0.12, 0.29)
2005	0.57 (0.54, 0.59)	0.53 (0.51, 0.56)	0.25 (0.18, 0.37)
2006	0.56 (0.53, 0.58)	0.53 (0.51, 0.55)	0.30 (0.22, 0.41)
2007	0.58 (0.55, 0.60)	0.55 (0.52, 0.57)	0.22 (0.15, 0.31)
2008	0.57 (0.55, 0.59)	0.54 (0.52, 0.56)	0.26 (0.19, 0.37)
2009	0.59 (0.57, 0.61)	0.57 (0.55, 0.59)	0.23 (0.16, 0.33)
2010	0.61 (0.59, 0.63)	0.59 (0.57, 0.61)	0.35 (0.26, 0.48)
2011	0.63 (0.61, 0.65)	0.62 (0.60, 0.64)	0.34 (0.25, 0.47)
2012	0.66 (0.64, 0.67)	0.64 (0.63, 0.66)	0.38 (0.27, 0.52)
2013	0.71 (0.69, 0.72)	0.70 (0.68, 0.71)	0.41 (0.30, 0.57)
2014	0.74 (0.73, 0.76)	0.74 (0.72, 0.76)	0.41 (0.29, 0.59)
2015	0.80 (0.78, 0.81)	0.79 (0.78, 0.81)	0.37 (0.24, 0.56)

All p values < 0.001. [†]Adjusted for age, sex, Townsend score and presence or absence of contraindications (binary).