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Nicola Adderley, Ronan Ryan and Tom Marshall

The role of contraindications in prescribing anticoagulants to patients with atrial fibrillation:

a cross-sectional analysis of primary care data in the UK

Abstract

Background
Underuse of anticoagulants in atrial fibrillation (AF) is an international problem, which has often been attributed to the presence of contraindications to treatment. No studies have assessed the influence of contraindications on anticoagulant prescribing in the UK.

Aim
To determine the influence of contraindications on anticoagulant prescribing in patients with AF in the UK.

Design and setting
Cross-sectional analysis of primary care data from 645 general practices contributing to The Health Improvement Network, a large UK database of electronic primary care records.

Method
Twelve sequential cross-sectional analyses were carried out from 2004 to 2015. Patients with a diagnosis of AF aged ≥35 years and registered for at least 1 year were included. Outcome measure was prescription of anticoagulant medication.

Results
Over the 12 study years, the proportion of eligible patients with AF with contraindications who were prescribed anticoagulants increased from 40.1% (95% confidence interval [CI] = 38.3 to 41.9) to 67.2% (95% CI = 65.6 to 68.8), and the proportion of those without contraindications prescribed anticoagulants increased from 42.1% (95% CI = 41.6 to 42.6) to 67.7% (95% CI = 67.2 to 68.1). In patients with a recent history of major bleeding or aneurysm, prescribing rates increased from 44.3% (95% CI = 42.2 to 46.5) and 34.8% (95% CI = 29.4 to 40.6) in 2004 to 71.7% (95% CI = 69.9 to 73.5) and 63.2% (95% CI = 58.3 to 67.8) in 2015, respectively, comparable with rates in patients without contraindications.

Conclusion
The presence or absence of recorded contraindications has little influence on the decision to prescribe anticoagulants for the prevention of stroke in patients with AF. The study analysis suggests that, nationally, 38 000 patients with AF with contraindications are treated with anticoagulants. This has implications for patient safety.

Keywords
anticoagulants; atrial fibrillation; contraindications; general practice; stroke, prevention; therapeutics.

INTRODUCTION

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and it is associated with a substantial increase in risk of ischaemic stroke.[1,2] Stroke risk is reduced by the use of anticoagulants.[3–8]

Anticoagulant prophylaxis has been recommended by the British Committee for Standards in Haematology since 1998 for patients with AF at elevated risk of stroke, and by the National Institute for Health and Care Excellence (NICE) since 2006.[9–11] In the UK, rates of anticoagulation remain low;[12–14] however, European studies suggest that high rates (>80%) of anticoagulation can be achieved.[15,16]

Underuse of anticoagulants is an international problem, which has often been attributed to the presence of contraindications to treatment, particularly bleeding or risk of bleeding.[13,17–21] Conversely, however, several studies in the US and Europe have found similar rates of prescribing between patients with and without contraindications.[22–24] To date, there have been no comparable studies carried out in the UK. Furthermore, there has been some inconsistency regarding which comorbidities are identified as contraindications to anticoagulant use. The Medicines and Healthcare products Regulatory Agency (MHRA) has defined contraindications to warfarin as: hypersensitivity to warfarin; haemorrhagic stroke; significant bleeding; pregnancy; within 72 hours of major surgery with risk of severe bleeding; within 48 hours postpartum; and drugs where interactions may lead to a significantly increased risk of bleeding.[25] In many studies, other comorbidities, such as risk of falls, and possible compliance issues are often included as contraindications; these may be better regarded as cautions for anticoagulant treatment rather than as absolute contraindications.[25,26]

The objective of this study was to investigate the relationship between contraindications and anticoagulant prescribing for AF in UK patients in primary care between 2004 and 2015.

METHOD

Data source

The Health Improvement Network is a database of anonymised electronic primary care records from UK general practices using Vision software. It includes coded data on patient characteristics, prescriptions, consultations, diagnoses, and primary care investigations for 3.6 million active patients registered at 587 active practices across the UK, with more than 85 million patient years of data.[27] Practices were eligible for inclusion in the study from the latest of the practice acceptable mortality recording date,[28] the Vision installation date, and the study start date (1 year prior to the first index date).

Study design

Twelve sequential cross-sectional analyses were performed on 1 May each year from

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How this fits in

Underuse of anticoagulants in atrial fibrillation (AF) is well recognised internationally and is often attributed to the presence of contraindications. However, to date, no analysis has investigated the extent to which contraindications influence anticoagulant prescribing in the UK. This study indicates that contraindications, as defined in UK guidance, have little influence on the clinician's decision to prescribe anticoagulants to patients with AF with moderate to high stroke risk. This has important implications for patient safety.

2004 to 2015 (index dates). All analyses were undertaken using Stata (version 13).

Analysis

Patients with a diagnosis of AF aged ≥35 years on the index date and registered at least 1 year prior to the index date were included in the analysis. The exposure of interest was the presence of contraindications to anticoagulants. Outcome was treatment with anticoagulants.

On each index date, the proportion of patients with AF with contraindications and the proportions of eligible patients prescribed anticoagulants with and without contraindications were calculated, with 95% confidence intervals (CI). *P*-values for trends over time were calculated using χ^2 tests; *P*-values for differences between proportions of binary variables were calculated using two-sample tests for proportions. In primary analysis, patients with a $CHADS_2$ score ≥1 (moderate or high stroke risk) were categorised as eligible for anticoagulant treatment. $CHADS_2$ score was used to define eligibility as it has been in use for longer than CHA_2DS_2-VASc;[29,30] in sensitivity analysis, patients with a CHA_2DS_2-VASc score ≥1 were categorised as eligible for anticoagulants.

Definitions of variables

A diagnosis of AF was defined by the presence of a clinical code for atrial fibrillation or atrial flutter at any time prior

Table 1. Baseline demographic data of patients with atrial fibrillation with and without contraindications to anticoagulants, 2004–2015

					Ethnicity[a] %				Townsend score[b] %					
Year	Contraindications	Population *n*	Age mean (SD)	Sex male, %	White	Asian	Black	Other	1	2	3	4	5	Missing
2004	Without	42 358	75.4 (11.1)	52.5	98.1	0.9	0.4	0.6	23.9	22.5	20.5	17.8	11.5	3.8
	With	2971	76.7 (9.9)	54.9	97.1	1.5	0.1	1.3	24.5	22.5	21.0	17.4	11.6	3.0
2005	Without	47 892	75.5 (11.2)	52.8	98.1	0.9	0.4	0.6	24.4	22.8	20.5	17.6	11.3	3.4
	With	3280	76.8 (9.8)	55.8	97.4	1.4	0.1	1.0	24.6	23.5	21.1	16.4	11.8	2.6
2006	Without	52 437	75.6 (11.3)	53.1	98.0	0.9	0.4	0.7	25.0	22.8	20.4	17.3	11.3	3.1
	With	3502	76.7 (9.9)	56.2	98.0	1.1	0.3	0.7	24.0	22.9	21.4	17.3	11.2	3.2
2007	Without	55 008	76.0 (11.1)	53.3	98.0	0.9	0.4	0.6	25.6	22.9	20.6	17.0	10.9	3.0
	With	3487	77.1 (9.8)	57.2	97.1	1.2	0.7	1.0	24.7	22.1	22.0	16.9	11.4	3.0
2008	Without	57 916	76.1 (11.0)	53.6	98.0	1.0	0.4	0.6	25.8	23.2	20.5	17.0	11.0	2.6
	With	3610	77.4 (9.5)	57.3	97.3	1.1	0.7	0.9	24.5	22.1	21.3	18.3	11.4	2.4
2009	Without	61 583	76.2 (11.0)	54.2	97.9	1.0	0.5	0.6	26.1	23.5	20.6	16.8	10.8	2.3
	With	3969	77.7 (9.5)	57.2	98.1	0.7	0.4	0.9	25.9	22.5	20.1	18.0	11.3	2.3
2010	Without	62 421	76.2 (11.0)	54.6	97.8	1.1	0.5	0.7	26.4	23.5	20.4	16.7	10.8	2.2
	With	4024	77.4 (9.8)	57.9	98.0	0.9	0.3	0.8	25.8	22.9	21.9	16.4	10.6	2.4
2011	Without	64 090	76.3 (11.1)	54.9	97.8	1.1	0.5	0.6	26.7	23.6	20.5	16.5	10.6	2.2
	With	4103	77.7 (9.6)	58.1	97.4	1.2	0.5	0.9	26.4	23.6	21.0	16.5	10.2	2.3
2012	Without	65 405	76.3 (11.1)	55.1	97.6	1.2	0.5	0.7	26.5	23.5	20.7	16.3	10.6	2.3
	With	4248	77.9 (9.7)	58.4	97.1	1.5	0.6	0.9	28.2	22.1	19.3	17.5	10.7	2.3
2013	Without	64 985	76.2 (11.2)	55.8	97.4	1.3	0.6	0.8	26.2	23.2	20.7	16.6	10.8	2.6
	With	4248	77.8 (10.0)	57.8	96.9	1.5	0.5	1.0	28.2	22.0	19.7	15.9	11.8	2.4
2014	Without	62 855	76.3 (11.2)	56.1	97.4	1.3	0.5	0.8	26.4	23.6	20.7	16.3	10.6	2.4
	With	4093	78.0 (9.7)	57.8	96.8	1.5	0.6	1.1	27.2	22.7	21.0	16.3	10.2	2.6
2015	Without	54 100	76.2 (11.2)	56.6	97.6	1.1	0.5	0.8	25.6	23.5	20.7	16.7	10.8	2.6
	With	3353	77.8 (10.0)	59.1	98.0	1.0	0.4	0.6	26.8	23.5	20.6	17.0	9.5	2.7

[a]Where recorded; ethnicity was missing in 59.2% of the patient records (decreasing from 74.4% in 2004 to 54.2% in 2015). [b]1 = Least deprived, 5 = Most deprived.

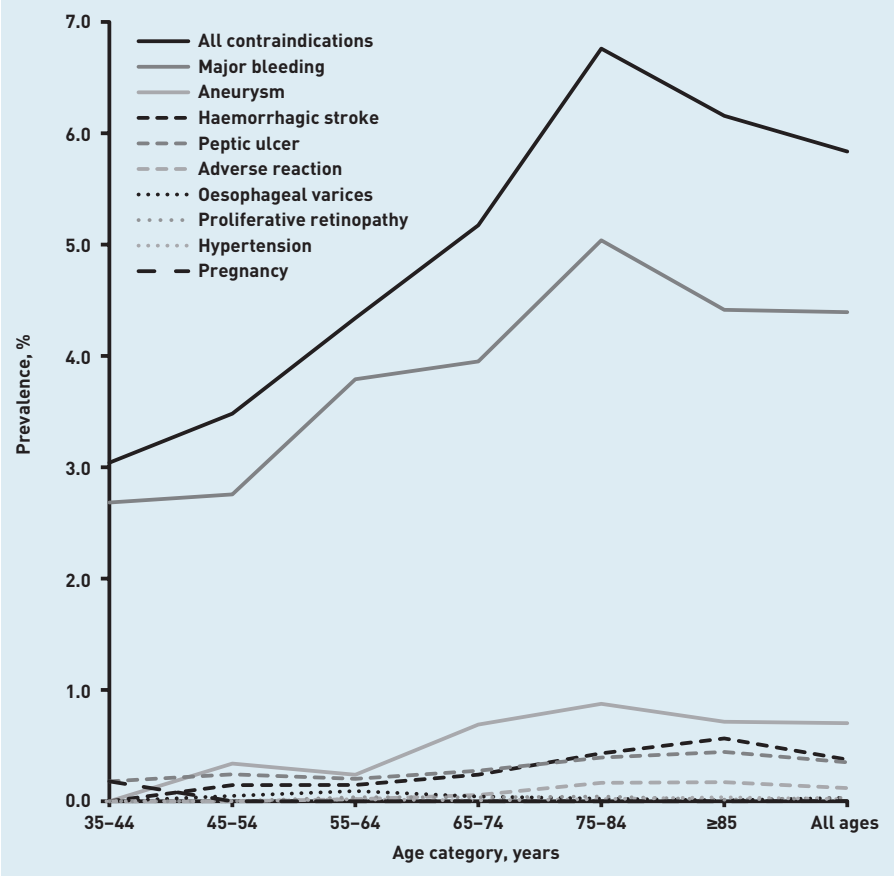

Figure 1. Prevalence of contraindications to anticoagulants in patients with atrial fibrillation by age category, 2015.

to the index date, excluding patients with a more recent clinical code indicating that AF had resolved. Current anticoagulant treatment was defined by a record of a relevant prescription within 90 days prior to the index date or a clinical code indicating the patient was receiving anticoagulant therapy within 365 days prior to the index date.

Contraindications to anticoagulants were defined in accordance with MHRA and NICE evidence.[25,26] Contraindications specific to anticoagulants other than warfarin, such as novel oral anticoagulants (NOACs) (for example, liver disease), were not included, as these do not preclude treatment with warfarin. Short-term contraindications (within 72 hours of surgery or 48 hours postpartum) and cautions for anticoagulant use were not included. Contraindications were defined as: a clinically coded diagnosis within the 2 years prior to the index date of haemorrhagic stroke, major bleeding (gastrointestinal, intracranial, intraocular, retroperitoneal), bleeding disorders (haemophilia, other haemorrhagic disorders, thrombocytopenia), peptic ulcer, oesophageal varices, aneurysm, or proliferative retinopathy; a record of allergy or adverse reaction to anticoagulants ever prior to the index date; a record of pregnancy in the 9 months prior to the index date; or severe hypertension with a mean (of the three most recent measures in the last 3 years prior to the index date) systolic blood pressure >200 mmHg or diastolic blood pressure >120 mmHg.

$CHADS_2$ scores were calculated by adding one point each for a history of congestive heart failure, hypertension, age ≥75 years, 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 each 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 each for age ≥75 years and history of stroke, TIA, or thromboembolism. History of congestive heart failure, stroke, TIA, thromboembolism, vascular disease, and diabetes were defined by a clinical code recorded ever prior to the index date, excluding patients with diabetes with a later record indicating diabetes resolved. Hypertension was defined as either 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 mmHg.

RESULTS

A total of 166 136 patients with AF from 645 practices were included in the study. As an individual could contribute to the analysis in more than 1 year, a total of 735 938 records of patients with AF were included in the analysis across the 12 index dates, with a median of 63 539 (interquartile range [IQR] = 56 696–67 571) patients per year. The mean age of patients with AF across all years was 76.2 (standard deviation [SD] 11.0) years; 54.7% (n = 402 354 out of 735 938) were male. Baseline characteristics are shown in Table 1: patients with AF with contraindications were on average 1.4 (95% CI = 1.3 to 1.5) years older and 2.3% (95% CI = 2.4 to 3.4) more were male.

Around 6% of patients had contraindications to anticoagulation and this changed little over the 12-year period (range = 5.8 to 6.6%). The most common contraindication was major bleeding: 4.4% (95% CI = 4.2 to 4.6) of patients with AF in 2015. The prevalence of individual contraindications remained reasonably constant from 2004 to 2015, except for declining frequency of peptic ulcer from 0.64% to 0.35% (P<0.001) and of severe hypertension from 0.22% to 0.02%

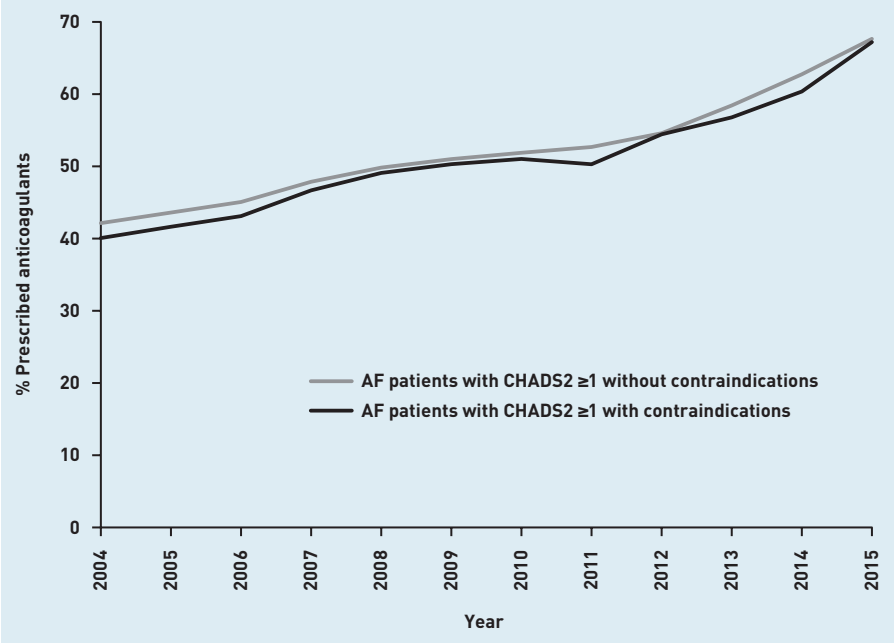

Figure 2. Proportion of patients with atrial fibrillation with and without contraindications who were prescribed anticoagulants, 2004–2015.

(P<0.001) (Appendix 1). The prevalence of all contraindications tended to increase with age (Figure 1).

The proportion of eligible patients (with a $CHADS_2$ score ≥1) prescribed anticoagulants increased from 2004 to 2015. However, in every year similar proportions with contraindications and without contraindications were prescribed anticoagulants (Figure 2). In 2004, 40.1% (95% CI = 38.3 to 41.9) of those with and 42.1% (95% CI = 41.6 to 42.6) of those without contraindications were prescribed anticoagulants; in 2015, this increased to 67.2% (95% CI = 65.6 to 68.8) and 67.7% (95% CI = 67.2 to 68.1), respectively (Appendix 2). The difference between the proportion of patients with and without contraindications who were prescribed anticoagulants in 2015 was not statistically significant: P = 0.595. In 2015, the interquartile range (IQR) for the proportion of eligible patients with AF prescribed anticoagulants by general practice was 52.6–80.0% in patients with contraindications and 61.8–72.4% in patients without contraindications.

Defining eligibility for anticoagulants using the CHA_2DS_2-VASc score (≥1) made no difference to the observed trends or to differences in treatment between those with and without contraindications (Appendix 3).

The proportions of patients with AF who were prescribed anticoagulants, and trends in prescribing, were similar between patients with the most common contraindications — major bleeding and aneurysm — and patients without contraindications (Appendix 4). In eligible patients with AF with a recent history of major bleeding or aneurysm, prescribing rates increased from 44.3% (95% CI = 42.2 to 46.5) and 34.8% (95% CI = 29.4 to 40.6) in 2004 to 71.7% (95% CI = 69.9 to 73.5) and 63.2% (95% CI = 58.3 to 67.8) in 2015, respectively. These were comparable to prescribing rates in eligible patients with AF without contraindications: 42.1% (95% CI = 41.6 to 42.6) and 67.7% (95% CI = 67.2 to 68.1) in 2004 and 2015 respectively. The proportion of patients with AF with less common contraindications who were prescribed anticoagulants was lower across the whole period but also increased over time. In 2015, anticoagulants were prescribed to 44.1% (95% CI = 32.8 to 56.1) with an adverse reaction, 54.3% (95% CI = 47.5 to 61.0) with gastrointestinal disorders, 38.1% (95% CI = 31.9 to 44.8) with haemorrhagic stroke, 54.5% (95% CI = 25.6 to 80.7) with severe hypertension, and 83.3% (95% CI = 58.2 to 94.7) with proliferative retinopathy.

Treatment of patients with AF with NOACs began in 2010 and their use has increased steadily since then (Appendix 5). In 2015, slightly more patients with contraindications were prescribed NOACs than vitamin K antagonists: 19.0% versus 17.4% (P = 0.061).

DISCUSSION

Summary

This analysis demonstrates that patients with AF with contraindications are just as likely to be prescribed anticoagulants as those without contraindications. The proportion of patients with AF with contraindications who are prescribed anticoagulants is increasing over time, mirroring the rise in prescribing to those without contraindications. This suggests that, in practice, the presence or absence of most contraindications has little or no influence on the clinician's decision to prescribe anticoagulants to patients with AF.

Strengths and limitations

The analysis was performed in a large general practice dataset that is generalisable to the UK population; the clinical data are routine and therefore comprise the information that GPs use for clinical decision making. AF diagnosis was often corroborated in the patient records, although it was not possible to confirm all diagnoses of AF; however, in a sample of 131 patients with AF diagnosed in UK primary care in 2006, 84% were found to have either a primary or secondary care electrocardiogram confirmation of their diagnosis.[31] Care was taken to exclude patients with 'AF resolved'.

Some anticoagulated patients may be omitted if they are managed entirely in hospital, and treatment rates may therefore be underestimated. However, this is attenuated by the inclusion of clinical codes for anticoagulant/international normalised ratio monitoring, in addition to prescription information, in the definition of anticoagulant use; furthermore, most anticoagulants are prescribed in primary care, and any underestimation is therefore likely to be small.

Most variables were defined by the presence of relevant clinical codes in the primary care record. Diagnoses that are part of the UK Quality and Outcomes Framework assessment are likely to be well recorded for most/all of the study period; clinically significant conditions, such as major bleed, which have important implications for prescribing of drugs other than anticoagulants, are also likely to be well recorded. However, recording of other medical conditions may be incomplete. There is no independent corroboration of the presence of contraindications, but the information used in the study is the same as that used by GPs for decision making, and contraindication rates are comparable with those found in other studies.[16,23] Some contraindications may be inaccurate, for example, haemorrhagic stroke may be reclassified as ischaemic stroke; however, diagnosis of haemorrhagic stroke is generally accurate in primary care records.[32] Some contraindications may be the result of previous anticoagulant treatment.

In addition to consideration of the presence/absence of contraindications, the decision to treat may also be influenced by cautions for anticoagulant use, such as the risk of falls or issues with treatment compliance. However, this should reduce rather than increase the likelihood of prescribing anticoagulants. Additionally, no information on patient preferences was available, although patients are often guided by GPs with regard to preventive medicine.[33]

Comparison with existing literature

Contraindications have often been cited as a reason for not prescribing anticoagulants.[17,19–21] However, this analysis suggests that contraindications do not stop clinicians from prescribing; this agrees with findings from studies in the US and Europe.[22–24] It is unclear why many patients with AF without contraindications are not prescribed anticoagulants, while patients with contraindications are.

Implications for research and practice

The study's findings have important implications for patient care. Alongside underuse of anticoagulants in patients with AF, there may be significant overtreatment of patients with contraindications. Based on the recorded prevalence of AF in recent data there are 1.03 million UK patients diagnosed with AF.[34,35] Of these, 59 000 (5.8%) have contraindications to anticoagulants, 57 000 (96%) of those with contraindications have a $CHADS_2$ score ≥1, and 38 000 (67.2%) are treated. This represents a significant concern for patient safety.

Although the balance of risks and benefits of using anticoagulants is favourable in patients with AF who do not have contraindications, it is unclear whether this also applies to patients with contraindications. Further work is needed to determine whether outcomes are worse among contraindicated patients with AF who are treated with anticoagulants than among those who are not, or whether the reduced stroke risk offsets any other potential adverse events. There is some recent evidence suggesting that resuming anticoagulant therapy may be beneficial in patients with AF who survive warfarin-related intracranial haemorrhage.[36,37]

Further work is needed to determine which patients with contraindications may still benefit from anticoagulant treatment. Qualitative research is needed in order to reveal the reasons why clinicians prescribe to patients with contraindications and why they do not prescribe to many patients without.

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Ethical approval

Research carried out using The Health Improvement Network data was approved by the NHS South-East Multicentre Research Ethics Committee (MREC) in 2003,[38] subject to independent scientific approval. Approval for this analysis was obtained on 2 April 2015 (SRC reference number 15THIN021).

Provenance

Freely submitted; externally peer reviewed.

Competing interests

The authors have declared no competing interests.

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Appendix 1. Prevalence of contraindications in patients with atrial fibrillation (AF), 2004–2015

		Contraindications (%)									
Year	All AF (*n*)	Any	Adverse reaction	Peptic ulcer	Major bleeding	Haemorrhagic stroke	Hypertension	Oesophageal varices	Aneurysm	Proliferative retinopathy	Pregnancy
2004	45 329	6.55	0.11	0.64	4.80	0.31	0.22	0.04	0.66	0.04	0.01
2005	51 172	6.41	0.17	0.55	4.74	0.33	0.16	0.04	0.67	0.05	0.00
2006	55 939	6.26	0.17	0.51	4.60	0.34	0.11	0.03	0.71	0.05	0.00
2007	58 495	5.96	0.15	0.49	4.38	0.33	0.09	0.02	0.69	0.04	0.00
2008	61 526	5.87	0.16	0.49	4.33	0.30	0.06	0.03	0.67	0.04	0.00
2009	65 552	6.05	0.14	0.46	4.53	0.27	0.06	0.03	0.75	0.04	0.01
2010	66 445	6.06	0.14	0.37	4.58	0.29	0.06	0.03	0.77	0.06	0.00
2011	68 193	6.02	0.13	0.43	4.55	0.30	0.05	0.03	0.70	0.05	0.00
2012	69 653	6.10	0.10	0.44	4.60	0.32	0.04	0.03	0.74	0.05	0.01
2013	69 233	6.14	0.13	0.40	4.60	0.35	0.03	0.03	0.75	0.04	0.01
2014	66 948	6.11	0.14	0.36	4.59	0.40	0.02	0.03	0.75	0.03	0.00
2015	57 453	5.84	0.12	0.35	4.39	0.37	0.02	0.03	0.70	0.03	0.00

Appendix 2. Proportion of eligible ($CHADS_2$ ≥1) patients with atrial fibrillation (AF) with and without contraindications prescribed anticoagulants, 2004–2015

	Patients with AF without contraindications				Patients with AF with contraindications				*P*-value for difference
	All	$CHADS_2$ ≥1	Anticoagulants		All	$CHADS_2$ ≥1	Anticoagulants		
Year	*n*	*n*	*n*	% (95% CI)	*n*	*n*	*n*	% (95% CI)	
2004	42 358	38 447	16 202	42.1 (41.6 to 42.6)	2971	2795	1120	40.1 (38.3 to 41.9)	0.0323
2005	47 892	43 692	19 051	43.6 (43.1 to 44.1)	3280	3115	1297	41.6 (39.9 to 43.4)	0.0325
2006	52 437	48 000	21 632	45.1 (44.6 to 45.5)	3502	3331	1436	43.1 (41.4 to 44.8)	0.0282
2007	55 008	51 008	24 416	47.9 (47.4 to 48.3)	3487	3340	1559	46.7 (45.0 to 48.4)	0.1821
2008	57 916	54 012	26 913	49.8 (49.4 to 50.2)	3610	3455	1696	49.1 (47.4 to 50.8)	0.3993
2009	61 583	57 689	29 424	51.0 (50.6 to 51.4)	3969	3815	1919	50.3 (48.7 to 51.9)	0.4002
2010	62 421	58 626	30 415	51.9 (51.5 to 52.3)	4024	3855	1967	51.0 (49.4 to 52.6)	0.3034
2011	64 090	60 259	31 745	52.7 (52.3 to 53.1)	4103	3953	1988	50.3 (48.7 to 51.8)	0.0036
2012	65 405	61 512	33 578	54.6 (54.2 to 55.0)	4248	4104	2234	54.4 (52.9 to 56.0)	0.8488
2013	64 985	60 995	35 640	58.4 (58.0 to 58.8)	4248	4098	2327	56.8 (55.3 to 58.3)	0.0384
2014	62 855	58 943	36 984	62.7 (62.4 to 63.1)	4093	3956	2388	60.4 (58.8 to 61.9)	0.0027
2015	54 100	50 677	34 286	67.7 (67.2 to 68.1)	3353	3226	2168	67.2 (65.6 to 68.8)	0.5947

Appendix 3. Proportion of patients with atrial fibrillation (AF) with a CHA_2DS_2-VASc ≥1 score with and without contraindications prescribed anticoagulants, 2004–2015

	Patients with AF without contraindications				Patients with AF with contraindications				*P*-value
	All	CHA_2DS_2-VASc ≥1	Anticoagulants		All	CHA_2DS_2-VASc ≥1	Anticoagulants		for
Year	*n*	*n*	*n*	% (95% CI)	*n*	*n*	*n*	% (95% CI)	difference
2004	42 358	40 309	16 848	41.8 (41.3 to 42.3)	2971	2897	1164	40.2 (38.4 to 42.0)	0.0881
2005	47 892	45 632	19 747	43.3 (42.8 to 43.7)	3280	3207	1340	41.8 (40.1 to 43.5)	0.0994
2006	52 437	50 020	22 338	44.7 (44.2 to 45.1)	3502	3428	1484	43.3 (41.6 to 45.0)	0.1191
2007	55 008	52 949	25 192	47.6 (47.2 to 48.0)	3487	3418	1595	46.7 (45.0 to 48.3)	0.3002
2008	57 916	55 925	27 677	49.5 (49.1 to 49.9)	3610	3549	1741	49.1 (47.4 to 50.7)	0.6165
2009	61 583	59 569	30 147	50.6 (50.2 to 51.0)	3969	3922	1973	50.3 (48.7 to 51.9)	0.7135
2010	62 421	60 383	31 080	51.5 (51.1 to 51.9)	4024	3956	2017	51.0 (49.4 to 52.5)	0.5538
2011	64 090	62 042	32 361	52.2 (51.8 to 52.6)	4103	4047	2019	49.9 (48.3 to 51.4)	0.0051
2012	65 405	63 342	34 169	53.9 (53.6 to 54.3)	4248	4187	2261	54.0 (52.5 to 55.5)	0.9431
2013	64 985	62 813	36 220	57.7 (57.3 to 58.0)	4248	4184	2363	56.5 (55.0 to 58.0)	0.1328
2014	62 855	60 690	37 535	61.8 (61.5 to 62.2)	4093	4040	2425	60.0 (58.5 to 61.5)	0.0210
2015	54 100	52 189	34 844	66.8 (66.4 to 67.2)	3353	3296	2196	66.6 (65.0 to 68.2)	0.8697

Appendix 4. Proportions of patients with atrial fibrillation with specific contraindications and a $CHADS_2$ score ≥1 who were prescribed anticoagulants, 2004–2015

	No contraindications		Any contraindication		Major bleeding		Haemorrhagic stroke		Aneurysm		Proliferative retinopathy		Severe hypertension		Gastrointestinal disorders[a]		Adverse reaction	
Year	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
2004	38 447	42.1 (41.6 to 42.6)	2795	40.1 (38.3 to 41.9)	2037	44.3 (42.2 to 46.5)	141	24.1 (17.7 to 31.9)	279	34.8 (29.4 to 40.6)	18	33.3 (15.4 to 57.9)	97	22.7 (15.4 to 32.1)	286	25.9 (21.1 to 31.3)	47	27.7 (16.7 to 42.2)
2005	43 692	43.6 (43.1 to 44.1)	3115	41.6 (39.9 to 43.4)	2290	45.4 (43.4 to 47.5)	169	27.8 (21.6 to 35.1)	326	38.0 (32.9 to 43.4)	26	46.2 (28.0 to 65.4)	77	22.1 (14.1 to 32.8)	285	25.3 (20.5 to 30.6)	85	25.9 (17.6 to 36.3)
2006	48 000	45.1 (44.6 to 45.5)	3331	43.1 (41.4 to 44.8)	2428	46.6 (44.6 to 48.6)	190	25.3 (19.6 to 31.9)	383	41.5 (36.7 to 46.5)	26	42.3 (24.9 to 61.9)	60	31.7 (21.1 to 44.5)	286	26.9 (22.1 to 32.4)	93	29.0 (20.7 to 39.1)
2007	51 008	47.9 (47.4 to 48.3)	3340	46.7 (45.0 to 48.4)	2440	50.9 (48.9 to 52.8)	191	31.9 (25.7 to 38.9)	392	43.4 (38.5 to 48.3)	22	45.5 (26.0 to 66.4)	50	36.0 (23.9 to 50.2)	280	26.4 (21.6 to 31.9)	89	27.0 (18.7 to 37.2)
2008	54 012	49.8 (49.4 to 50.2)	3455	49.1 (47.4 to 50.8)	2537	53.1 (51.1 to 55.0)	182	30.8 (24.5 to 37.9)	408	46.3 (41.5 to 51.2)	22	54.5 (33.6 to 74.0)	38	26.3 (14.6 to 42.6)	296	31.8 (26.7 to 37.3)	99	34.3 (25.6 to 44.3)
2009	57 689	51.0 (50.6 to 51.4)	3815	50.3 (48.7 to 51.9)	2839	54.6 (52.8 to 56.4)	177	26.6 (20.6 to 33.6)	480	49.2 (44.7 to 53.6)	25	40.0 (22.7 to 60.2)	41	29.3 (17.3 to 45.0)	300	25.0 (20.4 to 30.2)	90	30.0 (21.4 to 40.3)
2010	58 626	51.9 (51.5 to 52.3)	3855	51.0 (49.4 to 52.6)	2894	54.2 (52.4 to 56.0)	195	29.2 (23.3 to 36.0)	500	50.6 (46.2 to 55.0)	38	42.1 (27.4 to 58.3)	38	26.3 (14.6 to 42.6)	254	31.1 (25.7 to 37.1)	89	34.8 (25.6 to 45.3)
2011	60 259	52.7 (52.3 to 53.1)	3953	50.3 (48.7 to 51.8)	2977	53.2 (51.4 to 55.0)	205	25.4 (19.9 to 31.8)	468	52.1 (47.6 to 56.6)	33	54.5 (37.4 to 70.7)	33	45.5 (29.3 to 62.6)	299	32. 1 (27.0 to 37.6)	89	31.5 (22.6 to 41.9)
2012	61 512	54.6 (54.2 to 55.0)	4104	54.4 (52.9 to 56.0)	3078	57.9 (56.2 to 59.7)	222	24.8 (19.5 to 30.9)	510	55.1 (50.7 to 59.4)	34	50.0 (33.5 to 66.5)	25	28.0 (13.7 to 48.7)	315	36.8 (31.7 to 42.3)	69	39.1 (28.3 to 51.1)
2013	60 995	58.4 (58.0 to 58.8)	4098	56.8 (55.3 to 58.3)	3054	60.4 (58.7 to 62.2)	244	32.8 (27.2 to 38.9)	508	54.9 (50.6 to 59.2)	29	48.3 (30.7 to 66.3)	20	40.0 (21.0 to 62.6)	290	39.3 (33.8 to 45.1)	88	35.2 (25.9 to 45.8)
2014	58 943	62.7 (62.4 to 63.1)	3956	60.4 (58.8 to 61.9)	2959	64.5 (62.7 to 66.2)	265	35.8 (30.3 to 41.8)	486	56.4 (51.9 to 60.7)	23	69.6 (47.9 to 85.0)	16	50.0 (26.6 to 73.4)	252	45.6 (39.6 to 51.8)	91	33.0 (24.1 to 43.3)
2015	50 677	67.7 (67.2 to 68.1)	3226	67.2 (65.6 to 68.8)	2415	71.7 (69.9 to 73.5)	215	38.1 (31.9 to 44.8)	394	63.2 (58.3 to 67.8)	18	83.3 (58.2 to 94.7)	11	54.5 (25.6 to 80.7)	208	54.3 (47.5 to 61.0)	68	44.1 (32.8 to 56.1)

[a]*Peptic ulcer, oesophageal varices. N = denominator.*

Appendix 5. Type of anticoagulant prescribed to eligible patients with atrial fibrillation with and without contraindications to anticoagulants, 2004–2015

				Vitamin K antagonists				
		$CHADS_2$ ≥1	Prescribed anticoagulant	Warfarin	Parenteral	Other	NOACs	Multiple
Year	Contraindications	*n*	*n*	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
2004	With	2795	1120	1113 (99.4)	0	7 (0.6)	0	0
	Without	41 242	16 202	16 072 (99.2)	14 (0.1)	115 (0.7)	0	1 (0.0)
2005	With	3115	1297	1284 (99.0)	5 (0.4)	7 (0.5)	0	1 (0.1)
	Without	46 807	19 051	18 906 (99.2)	23 (0.1)	119 (0.6)	0	3 (0.0)
2006	With	3331	1436	1418 (98.7)	6 (0.4)	12 (0.8)	0	0
	Without	51 331	21 632	21 466 (99.2)	41 (0.2)	123 (0.6)	0	2 (0.0)
2007	With	3340	1559	1541 (98.8)	8 (0.5)	10 (0.6)	0	0
	Without	54 348	24 416	24 235 (99.3)	48 (0.2)	130 (0.5)	0	3 (0.0)
2008	With	3455	1696	1673 (98.6)	9 (0.5)	12 (0.7)	0	2 (0.1)
	Without	57 467	26 913	26 695 (99.2)	72 (0.3)	139 (0.5)	0	7 (0.0)
2009	With	3815	1919	1894 (98.7)	11 (0.6)	14 (0.7)	0	0
	Without	61 504	29 424	29 165 (99.1)	101 (0.3)	152 (0.5)	0	6 (0.0)
2010	With	3855	1967	1938 (98.5)	17 (0.9)	11 (0.6)	0	1 (0.1)
	Without	62 481	30 415	30 127 (99.1)	122 (0.4)	151 (0.5)	4 (0.0)	11 (0.0)
2011	With	3953	1988	1947 (97.9)	24 (1.2)	12 (0.6)	1 (0.1)	4 (0.2)
	Without	64 212	31 745	31 434 (99.0)	138 (0.4)	154 (0.5)	5 (0.0)	14 (0.0)
2012	With	4104	2234	2174 (97.3)	26 (1.2)	12 (0.5)	17 (0.8)	5 (0.2)
	Without	65 616	33 578	33 113 (98.6)	195 (0.6)	148 (0.4)	102 (0.3)	20 (0.1)
2013	With	4098	2327	2192 (94.2)	28 (1.2)	10 (0.4)	94 (4.0)	3 (0.1)
	Without	65 093	35 640	34 252 (96.1)	190 (0.5)	137 (0.4)	1034 (2.9)	27 (0.1)
2014	With	3956	2388	2113 (88.5)	39 (1.6)	6 (0.3)	227 (9.5)	3 (0.1)
	Without	62 899	36 984	33 579 (90.8)	211 (0.6)	127 (0.3)	3037 (8.2)	30 (0.1)
2015	With	3226	2168	1719 (79.3)	29 (1.3)	6 (0.3)	411 (19.0)	3 (0.1)
	Without	53 903	34 286	28 018 (81.7)	185 (0.5)	84 (0.2)	5959 (17.4)	40 (0.1)

NOACs = novel oral anticoagulants.