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Country and health expenditure are major predictors of withholding anticoagulation in atrial fibrillation patients at high risk of stroke

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ABSTRACT

Background Guidelines for patients with atrial fibrillation (AF) at high thromboembolic risk recommend oral anticoagulants (OACs) for preventing stroke and systemic embolism (SE). The reasons for guideline non-adherence are still unclear.

Aim The aim is to identify clinical, demographic and non-patient characteristics associated with withholding OAC in patients with AF at high stroke risk.

Methods Patients in the Global Anticoagulant Registry in the FIELD-AF, newly diagnosed with AF between March 2010 and August 2016, and with CHA_2DS_2-VASc Score≥2 (excluding sex), were grouped by OAC treatment at enrolment. Factors associated with OAC non-use were analysed by multivariable logistic regression.

Results Of 40 416 eligible patients, 12 126 (30.0%) did not receive OACs at baseline. Globally, OAC prescription increased over time, from 60.4% in 2010–2011 to 74.7% in 2015–2016. Country of enrolment was the major predictor for OAC withholding (χ^2–df=2576). Clinical predictors of OAC non-use included type of AF (χ^2–df=404), history of bleeding (χ^2–df=263) and vascular disease (χ^2–df=99). OACs were used most frequently around the age of 75 years and decreasingly with younger as well as older age beyond 75 years (χ^2–df=148). Non-cardiologists (χ^2–df=201) and emergency room physicians (χ^2–df=14) were less likely to prescribe OACs. OAC prescription correlated positively with country health expenditure.

Conclusions Approximately one out of three AF patients did not receive OAC, while eligible according to the guidelines. Country of enrolment was the major determinant of anticoagulation strategy, while higher country health expenditure was associated with lower likelihood of withholding anticoagulation.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Oral anticoagulants (OACs) are recommended for preventing stroke and systemic embolism in patients with atrial fibrillation (AF) and at high risk of thromboembolism. Previous studies identified common patient-level and physician-level barriers, as well as region-specific system-level barrier, to oral anticoagulant use but their relative importance has been unclear.

WHAT THIS STUDY ADDS

⇒ The likelihood of an eligible patient not receiving OAC treatment was associated mainly with country and country health expenditure and, independently, far less with patient-specific or care-specific factors.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The study highlights the importance of country-specific and socioeconomic factors for AF patients receiving guideline-recommended anticoagulation.

INTRODUCTION

Stroke is a leading cause of morbidity and mortality worldwide. Atrial fibrillation (AF), which affects approximately 2% of the population, is associated with a fivefold increased risk of ischaemic stroke.[1] Depending on the presence of risk factors, the annual incidence of stroke or systemic embolism (SE) is approximately 5% in AF patients not receiving anticoagulation.[2]

Evidence-based guidelines recommend the use of OAC in AF patients at a high risk of stroke/SE, with more recent guidelines recommending non-vitamin K oral anticoagulants (NOACs) over vitamin K antagonists.[3–6] But although prescriptions have increased globally since the introduction of NOACs, significant variability was reported across geographic regions.[7–11] Importantly, OACs continue to be underused in many countries.[12] Oral anticoagulants (OACs) should be used judiciously because they increase the risk of bleeding. Clinical guidelines therefore recommend the use of stroke risk prediction scores (eg, CHA_2DS_2-VASc Score) to provide individualised treatment.[3–6]

Although validated stroke risk prediction models are practical for everyday clinical application, limitations exist. I.e., CHA_2DS_2-VASc includes several well-known risk factors for stroke but does not incorporate additional patient characteristics such as echocardiographic and other imaging findings, or smoking, sleep apnoea, and hypertrophic cardiomyopathy which may influence treatment outcomes.[13] Furthermore, dichotomisation of continuous risk factors (eg, blood pressure, age) within the scores can lead to a misestimation of risk when factor values are close to the cut-off threshold. Bleeding risk scores, such as HAS-BLED,[14] are meant to alert physicians to bleeding risks which could, in turn, lead to modification of treatments, additional care and support to avoid bleeding. However, patients with high HAS-BLED scores often also have a high CHA_2DS_2-VASc Score.[15] Since these patients frequently do not receive OAC, it is possible that high bleed risk is regarded as a contraindication to anticoagulation, even in the group who would profit most from OAC use. Limitations such as these are likely to result in suboptimal treatment decisions.

Undertreatment of eligible patients despite evidence-based benefits is a problem which is well documented for Europe and North America.[16–22] Here, we investigated factors that might contribute to non-use of OAC in countries with different demographics, income and healthcare systems by modelling the likelihood of eligible patients not receiving OAC.

METHODS

Study design and participants

The Global Anticoagulant Registry in the FIELD-Atrial Fibrillation (GARFIELD-AF) is a prospective, observational, international study. Briefly, patients were recruited from 1215 sites in 35 countries, in 5 consecutive cohorts between March 2010 and August 2016.[23] Individuals aged≥18 years, with new-onset non-valvular AF (diagnosed within the previous 6 weeks according to standard local procedures), and with at least one investigator-determined risk factor for stroke, were eligible for inclusion. Patients with a transient reversible cause of AF[24] such as hyperthyroidism, or for whom follow-up was unlikely, were excluded. In the present analysis from the GARFIELD-AF registry, only patients with a CHA_2DS_2-VASc Score≥2 (excluding sex) were selected. Patients were followed up for a minimum of 2 years from enrolment. For this study, follow-up was censored at 2 years. Investigators obtained patient data from the medical record and patient interview. Investigators recorded the required data in a study-specific case record form (CRF), and a web-based system was used to collect CRF data.

Statistical analysis

Patients were categorised according to OAC use at enrolment, that is, no OAC use versus any vitamin K antagonist or non-vitamin NOAC (ie, dabigatran, apixaban, rivaroxaban or edoxaban). Descriptive statistics were expressed as median and IQRs for continuous variables, and absolute frequencies and percentages for categorical variables. Multivariable logistic regression analysis was performed using a prespecified set of covariates to determine factors associated with OAC non-use at baseline (online supplemental table S1). More specifically, three models were generated to establish associations with treatment decision: model 1 considered demographic patient characteristics, medical and cardiovascular history, lifestyle factors, vital signs, type of AF and care setting at diagnosis. An additional factor for model 2 was country of enrolment ('country'). For model 3, country-based expenditure on health per capita was included, expressed in international dollars at purchasing power parity (PPP).[25] In brief, PPPs are the rates of currency conversion that equalise the purchasing power of different currencies by eliminating the differences in price levels between countries. This indicator, having in a common currency and adjusted for price relatives, allows for meaningful cross-country comparisons. Each country has a unique value for health expenditure per year. Expenditure values for the years in which each country enrolled patients into GARFIELD-AF were averaged to provide one estimate per country of the 'country health expenditure'. All patient demographic and clinical variables reflect information collected at the time of enrolment.

Logistic least absolute shrinkage and selection operator regression determined predictors of receiving OAC based on data collected at enrolment. The relationship of the identified factors and the likelihood of OAC withholding is expressed by means of ORs and corresponding CI. The significance of a test diminishes as the number of categories (and thus df for the test) increases for a factor. As the numbers of categories varied from mostly 2 to up to 35, their relative importance was calculated as Wald χ^2–df.

The linearity assumption was evaluated for each continuous measure by applying restricted cubic splines. Multiple imputation[26] was applied to account for missing values and the obtained ORs represent the combinations from five imputed datasets. Statistical significance was assumed for a two-tailed probability level<0.05. Statistical analyses were performed using SAS Enterprise Guide V.8.2. The manuscript was drafted according to Strengthening the Reporting of Observational Studies in Epidemiology guidelines for observational studies.

RESULTS

Study population

The study flow diagram is shown in online supplemental figure S1. The enrolment period was March 2010–August 2016, with the final data cut-off on 30 June 2019. Among 52 057 patients enrolled in GARFIELD-AF, we excluded those with CHA_2DS_2-VASc Score<2 (excluding sex; n=11 018), or without available baseline treatment or follow-up information (n=623). Of the 40 416 patients

Table 1 Baseline characteristics by baseline anticoagulation*

Baseline characteristics	OAC treatment		P value †
	No (n=12 126)	Yes (n=28 290)	
Sex, n (col %)			
Male	6490 (53.5)	15 081 (53.3)	0.694
Female	5636 (46.5)	13 209 (46.7)	
Age, median (Q1; Q3), years	73.0 (66.0; 80.0)	74.0 (67.0; 80.0)	<0.001
Ethnicity, n (col %)			
White	6635 (56.3)	19 096 (69.2)	<0.001
Hispanic/Latino	874 (7.4)	1863 (6.7)	
Asian	4045 (34.3)	6122 (22.2)	
Black/mixed/other	234 (2.0)	529 (1.9)	
BMI, median (Q1; Q3), kg/m²	26.4 (23.5; 30.1)	27.2 (24.2; 31.1)	<0.001
Systolic blood pressure, median (Q1; Q3), mm Hg	132.0 (120.0; 145.0)	134.0 (120.0; 147.0)	<0.001
Diastolic blood pressure, median (Q1; Q3), mm Hg	80.0 (70.0; 87.0)	80.0 (70.0; 89.0)	<0.001
Pulse, median (Q1; Q3), bpm	82.0 (70.0; 102.0)	85.0 (71.0; 105.0)	<0.001
Type of atrial fibrillation, n (col %)			
Permanent	1371 (11.3)	4312 (15.2)	<0.001
Persistent	1315 (10.8)	4757 (16.8)	
Paroxysmal	3402 (28.1)	7137 (25.2)	
Unclassified	6038 (49.8)	12 084 (42.7)	
Care setting specialty at diagnosis, n (col %)			
Internal medicine/neurology/geriatrics	2614 (21.6)	5872 (20.8)	<0.001
Cardiology	7528 (62.1)	18 460 (65.3)	
Primary care/general practice	1984 (16.4)	3958 (14.0)	
Care setting location at diagnosis, n (col %)			
Hospital	7631 (62.9)	15 593 (55.1)	<0.001
Office/anticoagulation clinic/thrombosis centre	3204 (26.4)	9601 (33.9)	
Emergency room	1291 (10.6)	3096 (10.9)	
Medical history, n (col %)			
Heart failure	3430 (28.3)	7379 (26.1)	<0.001
Acute coronary syndrome	1955 (16.2)	3324 (11.8)	<0.001
Vascular disease	4523 (37.3)	7698 (27.2)	<0.001
Carotid occlusive disease	389 (3.2)	1028 (3.7)	0.032
VTE	225 (1.9)	901 (3.2)	<0.001
Prior to stroke/TIA/SE	1518 (12.5)	4179 (14.8)	<0.001
History of bleeding	578 (4.8)	553 (2.0)	<0.001
Hypertension	9854 (81.3)	23 670 (83.7)	<0.001
Hypercholesterolaemia	4779 (40.8)	12 788 (46.4)	<0.001
Diabetes	3136 (25.9)	7775 (27.5)	<0.001
Cirrhosis	93 (0.8)	125 (0.4)	<0.001
Moderate to severe CKD	1393 (12.0)	3546 (12.9)	0.008
Dementia	289 (2.4)	440 (1.6)	<0.001
Heavy alcohol user, n (col %)	226 (2.2)	425 (1.8)	0.009
Current smoker, n (col %)	1045 (9.5)	2214 (8.6)	0.006
Anticoagulant at baseline, n (col %)			
NOAC±AP	–	11 351 (40.1)	–
VKA±AP	–	16 939 (59.9)	
Antiplatelet treatment, n (col %)	8227 (67.8)	6580 (23.3)	<0.001
CHA_2DS_2-VASc Score, median (Q1; Q3)	4.0 (3.0; 5.0)	4.0 (3.0; 5.0)	0.405
HAS-BLED Score‡, median (Q1; Q3)	2.0 (1.0; 2.0)	1.0 (1.0; 2.0)	<0.001
GARFIELD-AF Death Score §, median (Q1; Q3)	4.6 (2.7; 8.2)	4.8 (2.9; 8.1)	<0.001

Continued

Table 1 Continued

Baseline characteristics	OAC treatment		P value †
	No (n=12 126)	Yes (n=28 290)	
GARFIELD-AF Stroke Score ¶, median (Q1; Q3)	1.4 (1.0; 2.0)	1.4 (1.0; 1.9)	<0.001
GARFIELD-AF Bleeding Score **, median (Q1; Q3)	1.8 (1.3; 2.6)	1.6 (1.2; 2.3)	<0.001

*This study analysed initial treatment of AF patients, regardless of the AF type, which might have been confirmed at later visits.
†Calculated using t-test or Wilcoxon-Mann-Whitney for continuous variables, as appropriate and χ^2 or Fisher's exact test for categorical variables, as appropriate.
‡The risk factor 'Labile INRs' is not included in the HAS-BLED Score as it is not collected at baseline. As a result, the maximum HAS-BLED Score at baseline is 8 points (not 9).
§Denotes the expected probability of death within 2 years from enrolment. To allow for comparability, the expected probability is computed assuming all patients received NOAC at baseline;.
¶The expected probability of developing a non-haemorrhagic stroke/SE within 2 years from enrolment. To allow for comparability, the expected probability is computed assuming all patients received NOAC at baseline;.
**The expected probability of developing a major bleeding within 2 years from enrolment. To allow for comparability, the expected probability is computed assuming all patients received NOAC at baseline.
AF, atrial fibrillation; AP, antiplatelet treatment; BMI, body mass index; CKD, chronic kidney disease; GARFIELD-AF, Global Anticoagulant Registry in the FIELD-AF; NOAC, non-vitamin K oral anticoagulant; OAC, oral anticoagulant; SE, systemic embolism; TIA, transient ischaemic attack; VKA, vitamin K antagonist treatment; VTE, venous thromboembolism.

included in the analysis, 12 126 (30.0%) did not receive OAC therapy at baseline.

Their baseline characteristics are shown in table 1.

Compared with those who received OAC, OAC non-users were more often of Asian ethnicity and diagnosed in an emergency room setting. OAC non-users also had higher HAS-BLED[14] and GARFIELD-AF bleeding scores[27] compared with OAC users. Moreover, OAC non-users had a lower prevalence of previous stroke, transient ischaemic attack (TIA) or SE and venous thromboembolism, and a higher prevalence of vascular disease, acute coronary syndrome, dementia and previous bleeding. The most commonly used antiplatelet drugs (AP) were aspirin (~80%), ADP receptor/P2Y12 inhibitors (~20%) and other Cox inhibitors (~10% of patients), irrespective of concomitant OAC therapy. A patient might take more than one type of AP. A comparison of the baseline characteristics of OAC-treated patients receiving vitamin K antagonist (VKA) versus NOAC is shown in online supplemental table S2.

Use of OAC and physician's explanations for withholding

Of all countries in GARFIELD-AF, China and India had the lowest rates of OAC use (≤40%), followed by Ukraine, Mexico, Russia, Brazil and South Korea (figure 1). At the same time, these countries had some of the highest proportions of patients receiving AP alone. Globally, the proportions of patients not receiving OAC at baseline decreased over time from 39.6% in cohort 1 (enrolment period 2010–2011) to 25.3% in cohort 5 (enrolment period 2015–2016). Overall, the proportion of patients on no antithrombotic therapy remained relatively unchanged over time (10.8% in 2010–2011; 9.0% in 2015–2016), but we observed a decline from 28.9% to 16.3% in patients receiving AP therapy only (figure 2), and differences in trends between countries (online supplemental table S3).

In 7370 (60.8%) of the 12 126 OAC-untreated patients, the main reason for withholding OAC was documented by the treating physician. Commonly cited reasons were

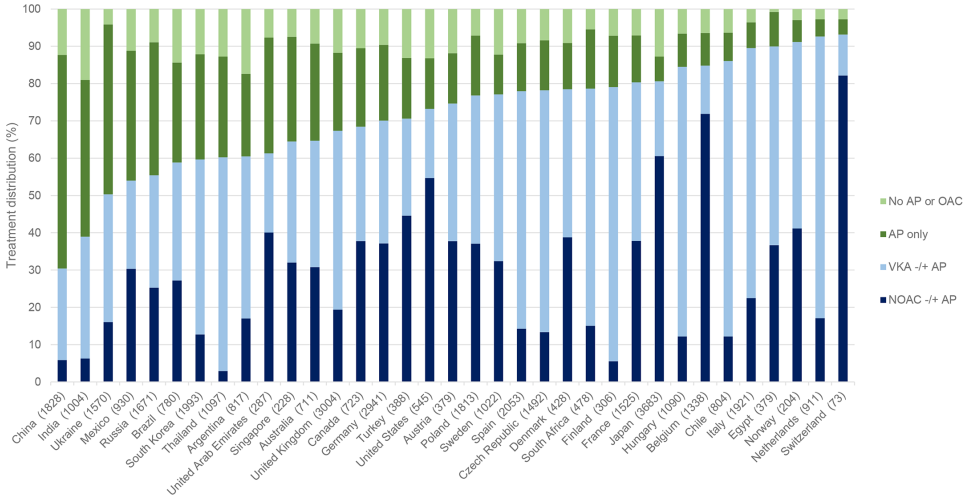

Figure 1 Distribution of treatments at baseline by country. Each column illustrates the proportion of eligible patients (CHA_2DS_2-VASc Score≥2) across all cohorts in the named country who received either an NOAC (dark blue), a VKA (light blue), only AP therapy (dark green) and no AP or OAC (light green). Countries are sorted from left to right in order of increasing OAC use (the combined blue colours). The total numbers of patients from each country are shown in brackets after the country name. AP, antiplatelet treatment; NOAC, non-vitamin K oral anticoagulant; OAC, oral anticoagulation; VKA, vitamin K antagonist treatment.

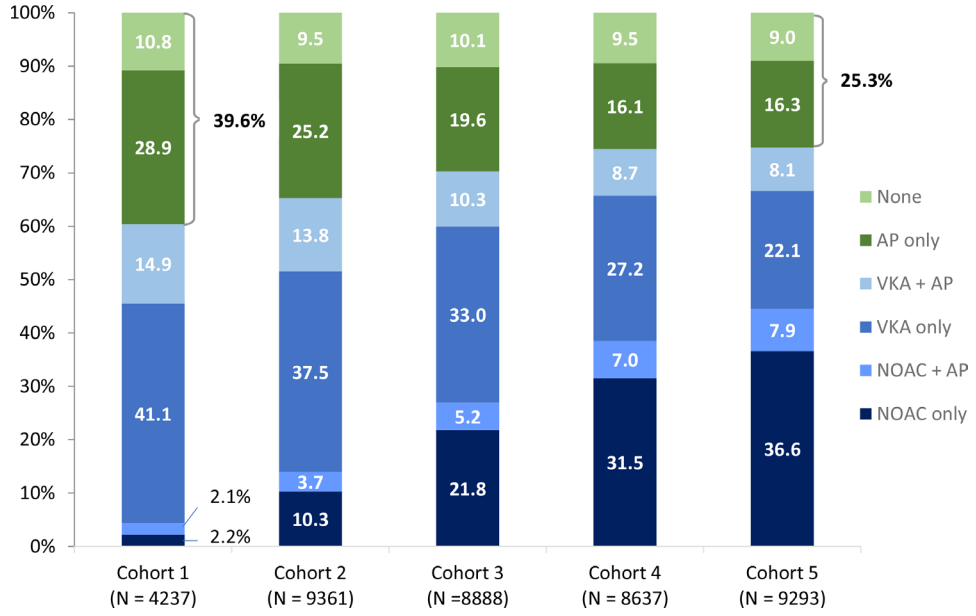

Figure 2 Distribution of baseline treatment by cohort of enrolment in patients eligible for OAC treatment. Blue colours: proportion of patients receiving OAC, green colours: proportion of patients not given OAC treatment. The periods for enrolment were: 2010–2011 (cohort 1), 2011–2013 (cohort 2), 2013–2014 (cohort 3), 2014–2015 (cohort 4), 2014–2015 (cohort 4). AP, antiplatelet treatment; NOAC, non-vitamin K oral anticoagulant; OAC, oral anticoagulation; VKA, vitamin K antagonist treatment.

high bleeding risk or previous bleeding event (14.8%), patient choice (12.8%) and low stroke risk (9.8%; despite a CHA_2DS_2-VASc≥2 excluding sex). The distribution of the reasons given for withholding OAC remained relatively stable throughout the five cohorts of enrolment (data not shown).

Predictors of OAC withholding

Three models were developed starting with clinical and demographic factors (model 1), then adding either country of enrolment (model 2), or the countries' yearly average health expenditure per person over the enrolment period (model 3). The included predictors and their relative significance, calculated as the Wald χ^2–df, are shown in table 2.

Cohort number (corresponding to period of enrolment) was the most significant predictor in model 1, and second most significant predictor in models 2 and 3. Country health expenditure was the most significant of all factors in model 3 (χ^2–df=832), but did not contain as much information as 'country' itself in model 2 (χ^2–df=2576). Model 2 (c-index=0.737) was more accurate in predicting treatment decision than model 1 (c-index=0.674) or model 3 (c-index=0.697).

Figure 3 shows ORs and relative significance of the predictors in model 2. The most significant clinical associations were type of AF (χ^2–df=404; OR for paroxysmal/new onset vs permanent/persistent=1.74; CI=1.65 to 1.84) and history of bleeding (χ^2–df=263; OR=2.95; CI=2.59 to 3.37). History of vascular disease (χ^2–df=99; OR=1.31; CI=1.24 to 1.39), history of stroke/TIA/SE (χ^2–df=88; OR=0.71; CI=0.66 to 0.76), history of venous thrombosis (χ^2–df=42; OR=0.59; CI=0.50 to 0.69), dementia (χ^2–df=40; OR=1.71; CI=1.45 to 2.02) and cirrhosis (χ^2–df=21; OR=2.03; CI=1.51 to 2.72) were additional factors associated with withholding OAC. The likelihood of withholding OACs decreased with increasing age up to age 75 and increased with increasing age in older individuals (χ^2–df=148). Non-cardiologists (χ^2–df=201) and physicians in emergency room hospital settings (χ^2–df=14) were less likely to prescribe OAC.

To test whether the introduction of NOACs modified the risk profile, we repeated the model in cohorts 3–5 only (online supplemental table S4). 'Country' remained the dominant component, and the order of 8/9 most significant predictors did not change. The exception was 'cohort' which moved from the second to the seventh position, due to a relatively small increase of OAC use from cohort 3–5 (figure 2).

Components of model 3 included country health expenditure information (online supplemental figure S2). Health expenditure per person, averaged across the years of patient enrolment, was the most significant predictor in this model. The corresponding OR (OR 0.79, 95% CI 0.78 to 0.80) indicates that a country health expenditure increase of US$1000 per person is associated to a 21% lower likelihood of withholding OAC in patients eligible for anticoagulation. The relationship between OAC use and health expenditure (averaged across the years of patient enrolment) appeared linear over the range of health expenditure in the included countries (from US$187 to US$8779 per person, data not shown). In our univariable analysis across countries, OAC use, either alone or in combination with AP, correlated

Table 2 Components of the models for predicting withholding OAC with corresponding Wald χ^2–df and model C-statistic

	Wald χ^2–df		
Variable	**Model 1**	**Model 2**	**Model 3**
Country	–	2576	–
Country health expenditure *	–	–	832
Cohort	518	569	623
Type of AF	393	404	489
History of bleeding	266	263	272
Care setting specialty	422	201	441
Age	154	148	143
Vascular disease	521	99	324
Prior to stroke/TIA/SE	96	88	86
VTE	44	42	38
Dementia	21	40	26
BMI	24	36	21
Cirrhosis	13	21	14
Hypertension	5	16	20
Race/ethnicity	665	14	304
Care setting location	156	14	22
Pulse	44	11	28
Hypercholesterolaemia	45	7	35
Moderate to severe CKD	11	4	7
Diabetes	10	3	9
Sex	9	0	0
C-statistic	0.674	0.737	0.697

Model 2 includes all the variables selected in model 1 with the addition of country information. Model 3 includes all the variables selected in model 1 with the addition of country's average health expenditure per person.
*Health expenditure, purchasing power parity (current international US$) represents the country's average for the period the country enrolled patients in GARFIELD-AF.
AF, atrial fibrillation; BMI, body mass index; CKD, chronic kidney disease; DF, df; GARFIELD-AF, Global Anticoagulant Registry in the FIELD-AF; SE, systemic embolism; TIA, transient ischaemic attack; VTE, venous thromboembolism.

positively with average health expenditure per person (online supplemental figure S3).

DISCUSSION

Our key finding is that country and health expenditure were far more significant predictors than ethnicity, demographic and clinical factors, or the period of cohort enrolment. The developed model including country of enrolment as variable had good predictive ability (c-statistic 0.737), whereas the two other models omitting this information performed moderately (c-statistic 0.679 and 0.674, respectively). It therefore appears that country of enrolment was a better predictor than the countries' health expenditure. The reasons warrant further investigation, but could include the existence of additional country-specific factors, independent of health expenditure. The Global Anticoagulation Roundtable reported that patient-level and physician-level barriers were common across the globe, while system-level barrier had a greater degree of regional variation. Among the latter were under-representation in studies of safety and efficacy, limited use of medical records, anticoagulation management dominated by haematology, socioreligious considerations (Middle East), large differences in access and care between private and public insurance (Latin America), and higher risks of OAC-related bleeding and intercranial haemorrhage (East Asia).[28]

Of note, patients were recruited for GARFIELD-AF during a time when NOACs were becoming more widely used due to their favourable harm/benefit profile and ease of administration compared with VKAs. This resulted in an overall increase of OAC use in the later cohorts, despite a decline in VKA prescriptions. Also declining was the proportion of patients treated with AP only, as reported previously.[7 29] Our findings suggest that country and health expenditure influence prescribing antithrombotic practices. Although beyond the scope of our analysis, this might be due, at least in part, to the higher costs of NOACs which is likely an important barrier for their use in low income countries. For example, a recent Chinese study found that self-paying and duration of AF for five or more years were negatively associated with OAC use, regardless of the risk of stroke.[30] Access to specialist advice and free NOAC treatment through a community dwelling Atrial Fibrillation Special Clinic significantly increased OAC use among high-risk patients.[31] We did indeed observe a relationship across countries between OAC use and average health expenditure per person. However, a model with country instead of health expenditure as additional component was more accurate, suggesting that the precise factors contributing to intercountry differences remain to be identified. Our results reinforce that the healthcare context is an important consideration when implementing of evidence into practice.

The enrolling physicians were asked to report the strongest reason why no OAC was given to a patient. Frequently named were a perceived high risk of bleeding and low risk of stroke. This is in contrast to the predicted risks of non-anticoagulated patients in this study, all of whom had a CHA_2DS_2-VASc Score≥2, and only 3.4% had a HAS-BLED Score>3 at baseline. According to their physicians, 9% of patients were deprived of OAC because they were already taking an antiplatelet drug, which is inferior to OAC for stroke prevention.[32] Fall risk accounted for 6% of the patients who were not anticoagulated despite major educational efforts to reassure physicians that stroke prevention outweighs the risk of from falling.[33] Differences in the perception of risks and benefits between medical specialities might contribute to the relative reluctance of physicians in primary care compared with cardiologists to initiate OAC treatment.[10] In addition, 13% of patients chose not to take OAC, which could have been due to adverse effects, personal costs or sociocultural factors.[8 34]

We and others previously reported withholding of OAC in 25%–30% of patients,[17] or off-label prescription of lower doses,[35 36] despite data supporting the efficacy

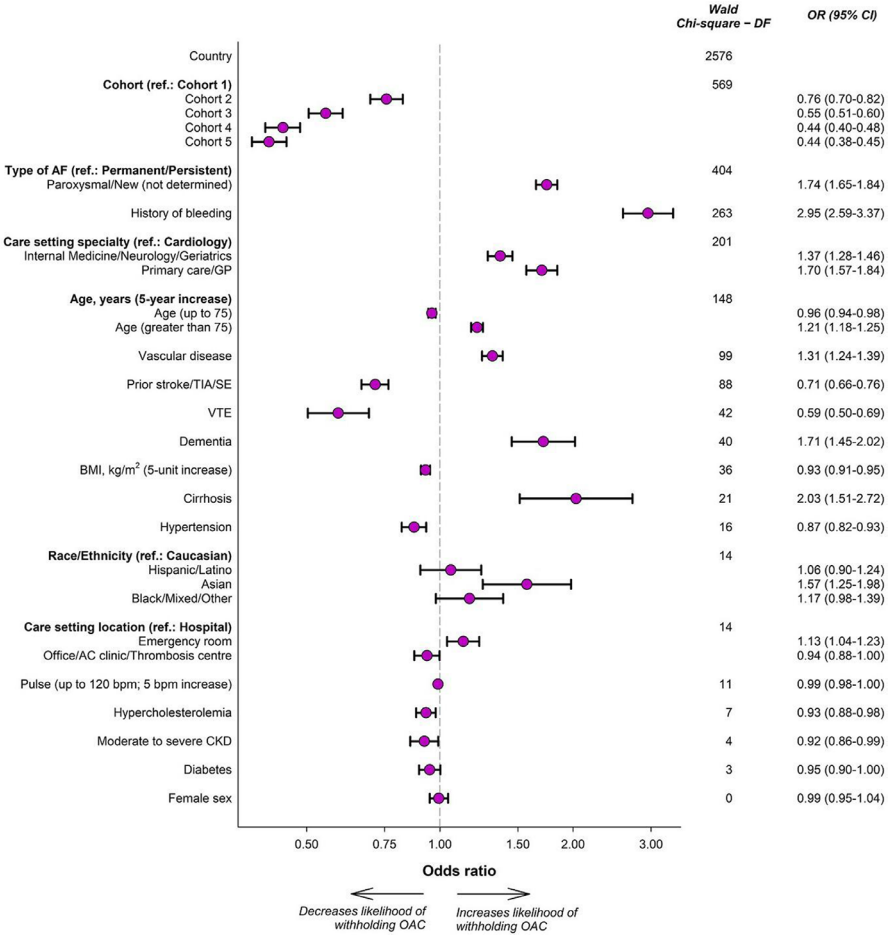

Figure 3 Components of the model predicting withholding of OAC. Associations refer to the model with the inclusion of country information (model 2). 'Country' represents the 'country' variable, rather than any of the 35 individual countries. Age and BMI are continuous; their ORs illustrate the increased likelihood of withholding OAC for every 5 units increase (eg, going from age 45 to 50 or age 80 to 85). AF, atrial fibrillation; BMI, body mass index; CKD, chronic kidney disease; GP, general practitioner; OAC, oral anticoagulation; SE, systemic embolism; TIA, transient ischaemic attack; VTE, venous thromboembolism.

and safety of OAC in AF. Moreover, the results of this study are in keeping with prior studies across the globe demonstrating that prior bleeding[37 38] and concurrent vascular disease, usually treated with antiplatelet therapy,[38 39] are strong risk factors for not using OACs in eligible patients.[38 39] Misperceptions regarding the efficacy of aspirin are a major reason for underutilising OAC.[40] A study performed in 2013 found that approximately 35% of AF patients on AP had no obvious indication for their use. Bleeding rates were significantly higher in patients on OAC plus aspirin compared with those on OAC alone.[41] Several studies also showed that patients with dementia and alcohol or drug abuse were less likely to receive OAC.[37 42]

OAC use in our patients peaked around 75 years and decreased both with younger and older age. Similarly, a report from the GLORIA-AF (Global Registry on Long-Term Oral Antithrombotic Treatment in Patients With Atrial Fibrillation) global registry found a slightly higher frequency of OAC treatment in patients aged 75–84 years compared with both younger and older patients.[43]

In contrast to a meta-analysis of observational studies by Baczek *et al*,[37] we did not find that the presence of renal disease was associated with a decreased likelihood of receiving OAC. However, substantial statistical heterogeneity existed in the meta-analysis. This could reflect variability in the populations studied, the methods used, or definitions of renal impairment, among other factors. Importantly, our study showed that non-patient specific factors, namely time of enrolment and country, were the most significant predictors of OAC treatment in AF patients at a high risk of stroke and SE. Similar observations were made for choice of NOAC versus VKA in AF patients not selected by CHA_2DS_2-VASc Score.[44]

Clinical predictors of OAC non-use not only differ with respect to their associated morbidity and mortality, but can be perceived differently by patients and physicians.[45–49] Some studies suggest that patients may have a higher risk tolerance for bleeding than stroke, whereas physicians may overestimate bleeding risk when making decisions about OACs.[48 50] Therefore, shared decision-making with AF patients including individualised

discussions about the potential benefits and harms of OAC for stroke prevention should be advocated.

A limitation of this study is that enrolment in GARFIELD-AF was completed in 2016 when many countries were still in the process of adopting the new guidelines for OAC use. However, recent studies have shown that OACs continue to be underused particularly in Asian countries.[12] Our analysis was limited to the examination of antithrombotic agents chosen by treating physicians for the initial treatment of newly diagnosed AF, and did not consider dosing, time on treatment, or possible changes in treatments over time. Moreover, because treatment was not randomly assigned, unobserved baseline confounding cannot be excluded and our inferences should not be interpreted as causal. We asked physicians for the reasons of their treatment choices, but did not collect data on whether a multidisciplinary team approach had been taken, or whether patients had been involved in the decision-making. Newer guidelines for the treatment of AF recommend these procedures, but the impact of this on NOAC use has not been investigated.

CONCLUSION

In summary, the present analysis of a large international prospective cohort of AF patients confirmed that OAC use was increasing globally over time over the period 2010–2016. Nevertheless, 30% of patients who would be expected to benefit from OAC did not receive them. Non-patient specific factors were the most powerful predictors of OAC non-use, including the country in which the patient was treated, country health expenditure and specialty of clinician managing the patient.

The study highlights the importance of country-specific and socioeconomic factors for AF patients receiving OAC treatment. We hope that its results will stimulate further research and discussion, leading to policy changes that improve patient access to appropriate stroke prevention worldwide.

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Contributors DS: conceptualisation, writing—original draft and writing—review/editing. FHV, AC-M, BJG, SG, AGGT and PA: conceptualisation and writing—review/editing. SV: methodology and formal analysis. JC and KAAF: conceptualisation, writing—review/editing and supervision. KP: conceptualisation, methodology, formal analysis and writing—review/editing. DS accepts responsibility as the guarantor of this study.

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Patient consent for publication Not applicable.

Ethics approval This study involves human participants. The GARFIELD-AF protocol was approved by independent ethics committees and/or hospital-based institutional review boards at hundreds of sites worldwide. A complete list can be made available on request. The study was conducted in accordance with the principles of the Declaration of Helsinki, the International Conference on Harmonization, Good Pharmaco epidemiological and Clinical Practice Guidelines, and local regulatory requirements. Participants gave informed consent to participate in the study before taking part.

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Data availability statement Data are available upon reasonable request. Requests for patient level data can be made to SV, head of statistics at the Thrombosis Research Institute (svirdone@tri-london.ac.uk). These requests should include a protocol summary and a summary of the statistical analysis plan. The request will be reviewed by the data sharing committee for approval and next steps will be discussed with the requestor.

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SUPPLEMENTARY MATERIAL

Figure S1. Flowchart for the selection of the study population. Of 52057 cases in the GARFIELD-AF registry, after exclusions and completion of follow-up, 28290 patients had received oral anticoagulation (OAC), 12126 no OAC at baseline.

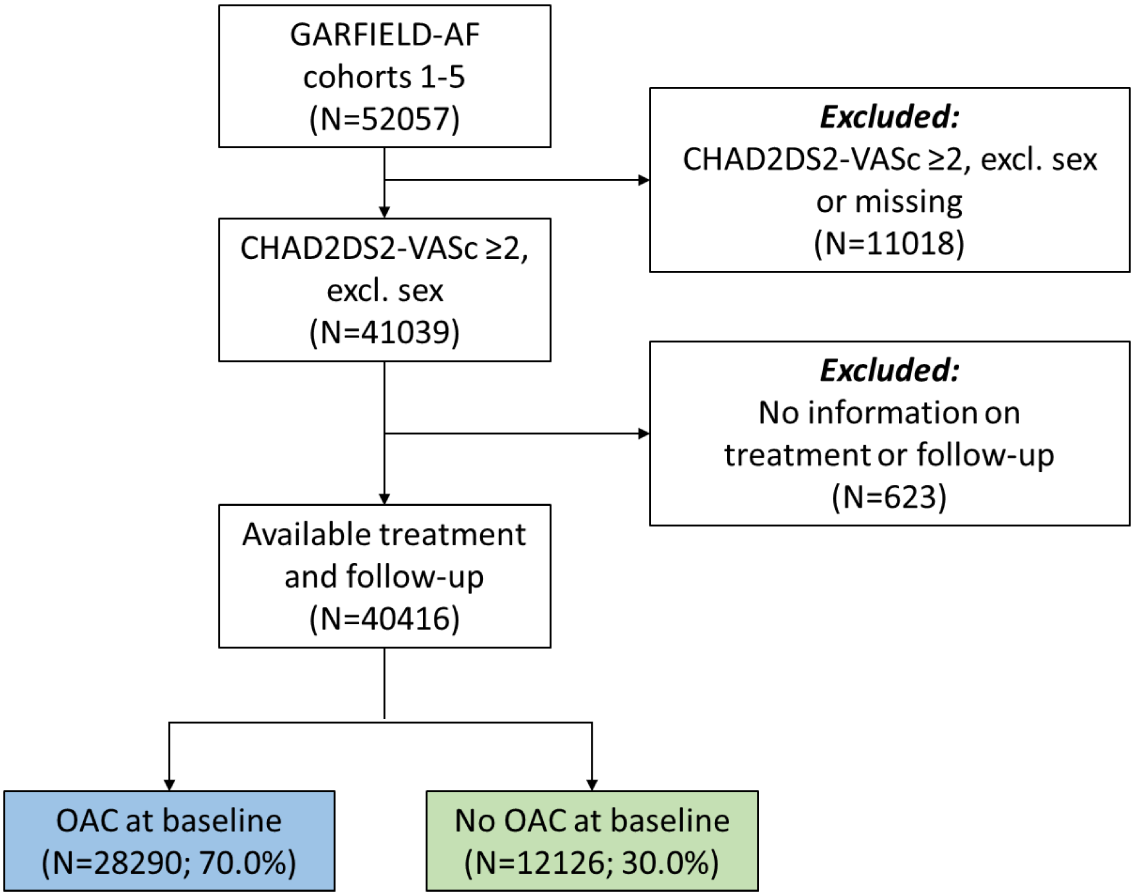

Figure S2. Components of the model predicting withholding of OAC. Associations reported refer to the model with the inclusion of health expenditure per capita information (Model 3)

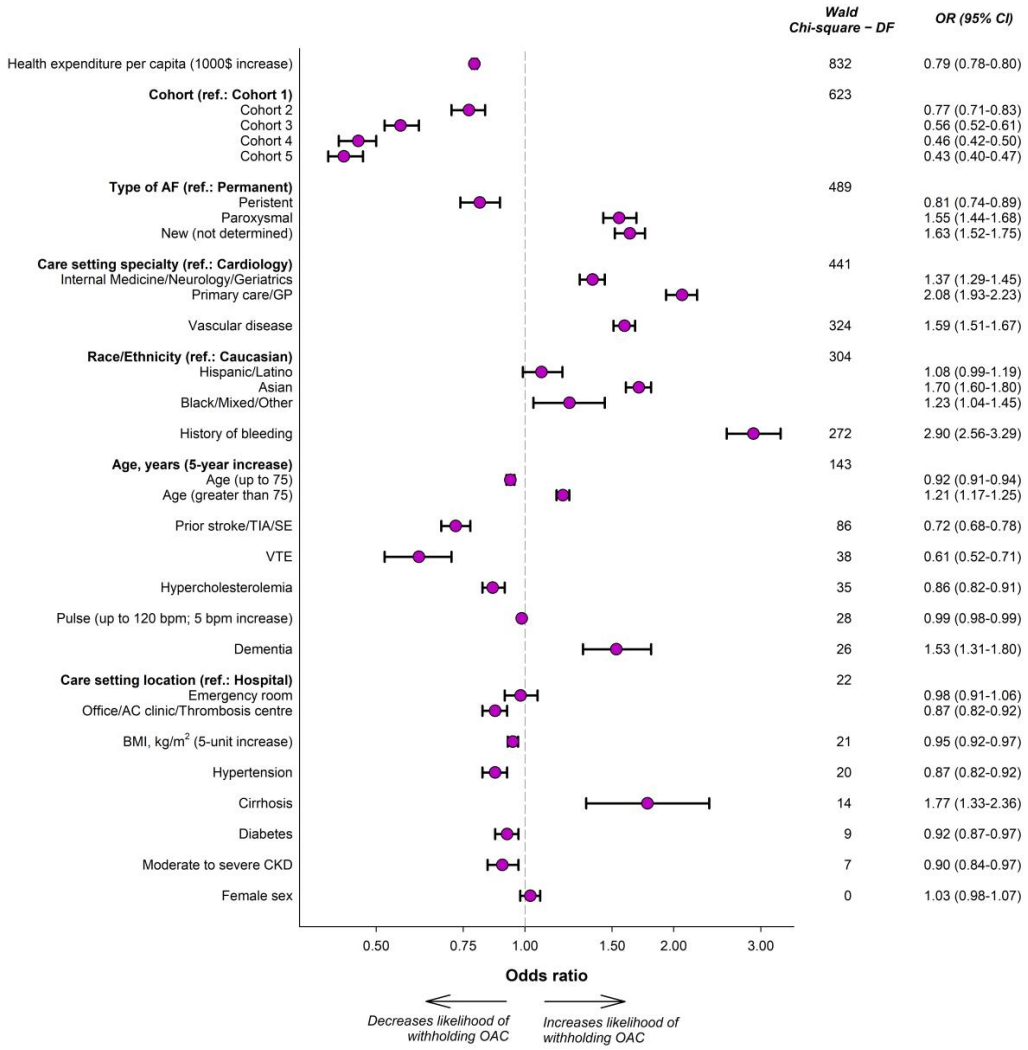

Figure S3. Relationship between country averages of health expenditure per person and OAC use (proportion of OAC-treated high-risk patients). Health expenditure, PPP (current international $) represents the country average between 2010-2016. Axes scales intersect at the averages across all countries and cohorts.

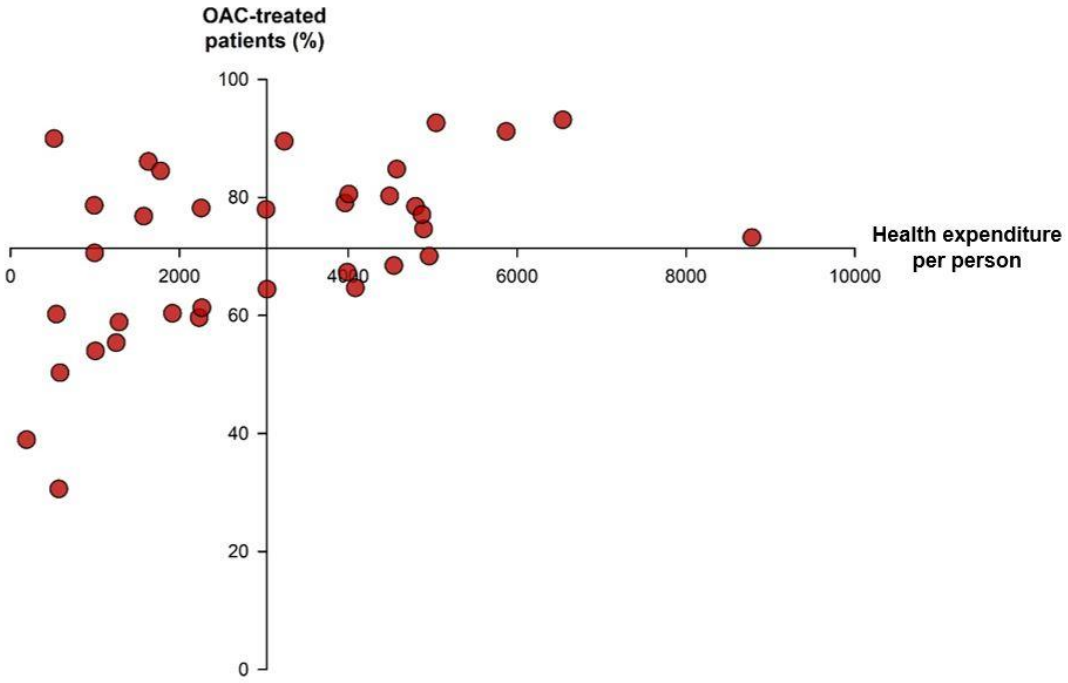

Table S1. List of potential predictors for the OAC withholding models. Variables for which no association with OAC withholding was found are shown in italics.

Demographics

- Sex
- Age
- Ethnicity/Ethnicity
- Country (only for model 2)

Medical and Cardiovascular History

- Hypertension
- Diabetes
- Moderate to severe CKD[1]
- History of bleeding[2]
- Heart failure
- Acute coronary syndromes
- Carotid occlusive disease
- Venous thromboembolism
- Vascular disease[3]
- Prior stroke/TIA/SE
- Hypercholesterolemia

Lifestyle factors

- Current smoking
- Heavy alcohol consumption[4]

Vital signs

- BMI (kg/m^2)
- Pulse (bpm)
- Systolic blood pressure (mmHG)
- Diastolic blood pressure (mmHG)

Atrial fibrillation diagnosis

- Type of atrial fibrillation[5]

Care setting at diagnosis

- Care setting specialty
- Care setting location

Other

- Cohort of enrolment[6]

• Cirrhosis • Hyperthyroidism • Hypothyroidism • Dementia	• Health expenditure per person, PPP, in current international $ (only for model 3)

[1] Defined as CKD stage III to V
[2] Defined as a previous occurrence of bleeding of any severity and type
[3] Defined as peripheral vascular disease and/or coronary artery disease
[4] Investigator-defined
[5] Classified as paroxysmal, persistent, permanent or unclassified
[6] Cohort 1 (period of enrolment 2010-2011), Cohort 2 (2011-2013), Cohort 3 (2013-2014), Cohort 4 (2014-2015), Cohort 5 (2015-2016)

BMI: body mass index, CKD: chronic kidney disease, OAC: oral anticoagulation, SE: systemic embolism, TIA: transient ischemic attack, PPP: purchasing power parity

Table S2. Baseline characteristics among patients treated with OAC at baseline by baseline OAC treatment[1]

Baseline characteristics	OAC treatment		P-value[2]
	VKA (n = 16939)	NOAC (N = 11351)	
Sex, n (col %)			
Male	9024 (53.3)	6057 (53.4)	0.885
Female	7915 (46.7)	5294 (46.6)	
Age, median (Q1; Q3), years	73.0 (67.0;79.0)	74.0 (68.0;80.0)	<0.001
Ethnicity, n (col %)			
White	11748 (70.9)	7348 (66.6)	<0.001
Hispanic/Latino	1283 (7.7)	580 (5.3)	
Asian	3244 (19.6)	2878 (26.1)	
Black/Mixed/Other	296 (1.8)	233 (2.1)	
BMI, median (Q1; Q3), kg/m²	27.5 (24.4;31.2)	26.8 (23.9;30.7)	<0.001
Systolic blood pressure, median (Q1; Q3), mmHg	134.0 (120.0;147.0)	133.0 (120.0;146.0)	0.427
Diastolic blood pressure, median (Q1; Q3), mmHg	80.0 (70.0;90.0)	80.0 (70.0;88.0)	<0.001
Pulse, median (Q1; Q3), bpm	85.0 (72.0;105.0)	84.0 (70.0;108.0)	0.528
Type of atrial fibrillation, n (col %)			
Permanent	2932 (17.3)	1380 (12.2)	<0.001
Persistent	2903 (17.1)	1854 (16.3)	
Paroxysmal	3540 (20.9)	3597 (31.7)	
Unclassified	7564 (44.7)	4520 (39.8)	
Care setting specialty at diagnosis, n (col %)			
Internal medicine/Neurology/Geriatrics	3759 (22.2)	2113 (18.6)	<0.001
Cardiology	10397 (61.4)	8063 (71.0)	

Primary care/general practice	2783 (16.4)	1175 (10.4)	
Care setting location at diagnosis, n (col %)			
Hospital	9829 (58.0)	5764 (50.8)	
Office/Anticoagulation clinic/Thrombosis centre	5082 (30.0)	4519 (39.8)	<0.001
Emergency room	2028 (12.0)	1068 (9.4)	
Medical history, n (col %)			
Heart failure	4544 (26.8)	2835 (25.0)	<0.001
Acute coronary syndrome	2050 (12.1)	1274 (11.3)	0.026
Vascular disease	4770 (28.2)	2928 (25.8)	<0.001
Carotid occlusive disease	611 (3.6)	417 (3.7)	0.741
VTE	636 (3.8)	265 (2.3)	<0.001
Prior stroke/TIA/SE	2587 (15.3)	1592 (14.0)	0.004
History of bleeding	310 (1.8)	243 (2.1)	0.063
Hypertension	14336 (84.7)	9334 (82.3)	<0.001
Hypercholesterolemia	7609 (46.1)	5179 (46.8)	0.0206
Diabetes	4847 (28.6)	2928 (25.8)	<0.001
Cirrhosis	85 (0.5)	40 (0.4)	0.066
Moderate to severe CKD	2242 (13.7)	1304 (11.8)	<0.001
Dementia	196 (1.2)	244 (2.2)	<0.001
Heavy alcohol user, n (col %)	258 (1.8)	167 (1.8)	0.925
Current smoker, n (col %)	1307 (8.4)	907 (8.8)	0.293
Antiplatelet treatment, n (col %)	4345 (25.7)	2235 (19.7)	<0.001
CHA_2DS_2-VASc score, median (Q1; Q3)	4.0 (3.0;5.0)	4.0 (3.0;4.0)	0.003
HAS-BLED score [3], median (Q1; Q3)	1.0 (1.0;2.0)	1.0 (1.0;2.0)	<0.001
GARFIELD-AF death score [4], median (Q1; Q3)	6.0 (3.7; 10.0)	4.8 (2.9; 8.1)	<0.001
GARFIELD-AF stroke score [5], median (Q1; Q3)	1.7 (1.3; 2.4)	1.4 (1.0; 2.0)	<0.001
GARFIELD-AF bleeding score [6], median (Q1; Q3)	2.3 (1.7; 3.2)	1.6 (1.2; 2.3)	<0.001

[1] This study analyzed initial treatment of AF patients, regardless of the AF type which might have been confirmed at later visits;
[2]Calculated using T-test or Wilcoxon-Mann-Whitney for continuous variables, as appropriate, and Chi-squared or Fisher's exact test for categorical variables, as appropriate;
[3] The risk factor 'Labile INRs' is not included in the HAS-BLED score as it is not collected at baseline. As a result, the maximum HAS-BLED score at baseline is 8 points (not 9).
[4] Denotes the expected probability of death within two years from enrolment.
[5] Denotes the expected probability of developing a non-hemorrhagic stroke/SE within two years from enrolment.
[6] Denotes the expected probability of developing a major bleeding within two years from enrolment.
AP: anti-platelet treatment, BMI: body mass index, CKD: chronic kidney disease, NOAC: non-vitamin K oral anticoagulant, OAC: oral anti-coagulant, SE: systemic embolism, TIA: transient ischemic attack, VTE: venous thromboembolism

Table S3. Proportion (%) of patients in each country not on anticoagulant treatment at baseline, by cohort of enrolment

Country	Cohort 1 (2010-2011)	Cohort 2 (2011-2013)	Cohort 3 (2013-2014)	Cohort 4 (2014-2015)	Cohort 5 (2015-2016)
Argentina	-	37.40	43.92	37.28	38.10
Australia	35.63	46.15	40.45	29.13	23.93
Austria	30.25	29.03	25.00	16.67	19.67
Belgium	-	20.25	16.58	12.88	10.22
Brazil	38.75	41.01	40.74	44.12	40.00
Canada	31.75	32.91	29.34	35.59	28.37
Chile	-	25.66	15.07	7.41	9.17
China	76.84	77.58	68.98	64.12	61.68
Czech Republic	-	26.65	21.01	22.60	16.71
Denmark	33.33	27.01	19.51	17.39	10.09
Egypt	-	-	-	6.82	11.00
Finland	29.58	26.36	13.13	12.5	0.00
France	23.48	18.88	22.68	13.97	20.17
Germany	45.72	37.36	19.33	15.62	17.00
Hungary	-	18.82	13.54	14.83	14.92
India	-	57.96	62.45	48.15	69.35
Italy	9.92	11.63	9.16	13.23	7.71
Japan	32.34	23.33	17.37	18.14	18.18
Mexico	60.74	47.58	35.48	38.36	38.75
Netherlands	10.71	10.63	5.64	4.84	2.56
Norway	11.43	1.82	8.33	13.04	21.05
Poland	33.99	32.38	21.69	11.90	10.73
Russia	-	52.52	46.48	41.32	35.75
Singapore	-	43.75	37.04	27.91	33.73
South Africa	-	21.05	27.84	22.86	16.08
South Korea	54.94	42.74	38.50	25.61	27.71
Spain	25.84	21.79	22.53	23.31	15.72
Sweden	36.49	32.81	19.91	11.58	9.59
Switzerland	-	-	-	9.52	5.77
Thailand	-	38.52	38.58	43.29	38.24
Turkey	-	-	-	33.10	27.24
Ukraine	-	62.00	51.34	42.77	42.70
United Arab Emirates	-	-	40.00	43.00	32.18
United Kingdom	40.32	43.49	38.50	24.29	24.07
United States	-	-	17.98	27.13	30.14

Table S4. Components of the model predicting withholding of OAC in cohorts 3 to 5, recruited during the time when NOACs became widely available. Age and BMI are continuous. Their odds ratios illustrate the increased likelihood of withholding OAC for every five units increase (e.g., going from age 45 to 50, or age 80 to 85).

Variable	Wald Chi-square − DF	Odds ratio (95% CI)
Country	1622	
Type of AF (ref.: Permanent/Persistent)	243	
Paroxysmal/New onset (unclassified)		1.76 (1.64-1.89)
History of bleeding	186	3.14 (2.67-3.70)
Care setting specialty (ref.: Cardiology)	120	
Internal Medicine/Neurology/Geriatrics		1.39 (1.28-1.51)
Primary care/GP		1.70 (1.53-1.90)
Age, five-years increase	106	
Age up to 75		0.94 (0.92-0.96)
Age greater than 75		1.22 (1.18-1.27)
Vascular disease	83	1.37 (1.28-1.47)
Cohort (ref.: Cohort 3, 2013-2014)	73	
Cohort 4 (2014- 2015)		0.79 (0.74-0.85)
Cohort 5 (2015 -2016)		0.74 (0.69-0.79)
Prior stroke/TIA/SE	44	0.73 (0.67-0.80)
Care setting location (ref.: Hospital)	33	
Emergency room		1.12 (1.01-1.25)
Office/AC clinic/Thrombosis centre		0.80 (0.74-0.88)
BMI, 5 kg/m^2 increase	23	0.93 (0.90-0.96)
VTE	19	0.62 (0.50-0.76)

Cirrhosis	15	2.13 (1.47-3.08)
Hypertension	14	0.86 (0.79-0.93)
Dementia	13	1.50 (1.21-1.85)
Hypercholesterolemia	6	0.92 (0.86-0.98)
Diabetes	2	0.95 (0.88-1.02)
Race/Ethnicity (ref.: Caucasian)	2	
Hispanic/Latino		1.19 (0.97-1.46)
Asian		1.27 (0.95-1.69)
Black/mixed/other		1.03 (0.82-1.30)

OAC: oral anticoagulation, AF: atrial fibrillation, BMI: body mass index, CKD: chronic kidney disease, GP: general practitioner, SE: systemic embolism, TIA: transient ischemic attack, VTE: venous thromboembolism