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ORIGINAL RESEARCH

Sex Differences in Oral Anticoagulation Therapy in Patients Hospitalized With Atrial Fibrillation: A Nationwide Cohort Study

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BACKGROUND: Important disparities in the treatment and outcomes of women and men with atrial fibrillation (AF) are well recognized. Whether introduction of direct oral anticoagulants has reduced disparities in treatment is uncertain.

METHODS AND RESULTS: All patients who had an incident hospitalization from 2010 to 2019 with nonvalvular AF in Scotland were included in the present cohort study. Community drug dispensing data were used to determine prescribed oral anticoagulation therapy and comorbidity status. Logistic regression modeling was used to evaluate patient factors associated with treatment with vitamin K antagonists and direct oral anticoagulants. A total of 172 989 patients (48% women [82 833 of 172 989]) had an incident hospitalization with nonvalvular AF in Scotland between 2010 and 2019. By 2019, factor Xa inhibitors accounted for 83.6% of all oral anticoagulants prescribed, while treatment with vitamin K antagonists and direct thrombin inhibitors declined to 15.9% and 0.6%, respectively. Women were less likely to be prescribed any oral anticoagulation therapy compared with men (adjusted odds ratio [aOR], 0.68 [95% CI, 0.67–0.70]). This disparity was mainly attributed to vitamin K antagonists (aOR, 0.68 [95% CI, 0.66–0.70]), while there was less disparity in the use of factor Xa inhibitors between women and men (aOR, 0.92 [95% CI, 0.90–0.95]).

CONCLUSIONS: Women with nonvalvular AF were significantly less likely to be prescribed vitamin K antagonists compared with men. Most patients admitted to the hospital in Scotland with incident nonvalvular AF are now treated with factor Xa inhibitors and this is associated with fewer treatment disparities between women and men.

Key Words: atrial fibrillation ■ oral anticoagulation therapy ■ sex differences

Women are at increased risk of ischemic stroke caused by atrial fibrillation (AF); therefore, current clinical practice guidelines recommend use of risk stratification scores that incorporate female sex to guide use of oral anticoagulation therapy.[1–4] Despite this guidance, women with AF remain undertreated and their outcomes are poorer compared with men.[5,6]

Vitamin K antagonists, mainly warfarin, have been the mainstay for stroke prophylaxis in patients with AF for many decades, but, in the past few years, direct oral anticoagulants (DOACs) have been introduced into clinical practice as alternatives. The safe use of warfarin requires careful dose titration to maintain patients within a narrow therapeutic range of international normalized ratio (INR), but this is challenging, with many registries demonstrating suboptimal time in therapeutic range (TTR), resulting in higher rates of mortality, major bleeding, and stroke.[7,8] Conversely, all DOACs have a predictable therapeutic effect without need for dose titration and regular anticoagulation monitoring. In a

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CLINICAL PERSPECTIVE

What Is New?

- In a contemporary nationwide cohort study using individual patient data linkage, more than one-third of patients admitted to the hospital in Scotland with incident nonvalvular atrial fibrillation remained untreated with any oral anticoagulation.
- Women were less likely to receive oral anticoagulation therapy than men, and the disparity was primarily attributable to vitamin K antagonists, while there was less disparity in treatment with direct factor Xa inhibitors.
- Women who were not treated with oral anticoagulation therapy experienced the highest rates of subsequent major adverse cardiovascular events and all-cause mortality, with no significant difference in rates of bleeding.

What Are the Clinical Implications?

- Most patients admitted to the hospital with incident nonvalvular atrial fibrillation are now treated with direct factor Xa inhibitors and this is associated with fewer treatment disparities between women and men and in older, more comorbid patients.
- If these trends continue, disparities in oral anticoagulation therapy between women and men with atrial fibrillation may be eliminated through increased treatment with direct factor Xa inhibitors.

Nonstandard Abbreviations and Acronyms

ATC	Anatomical Therapeutic Chemical classification system
BARC	Bleeding Academic Research Consortium
CCI	Charlson Comorbidity Index
DOAC	direct oral anticoagulant
GRO	General Register of Scotland
MACE	major adverse cardiovascular events
NHS	National Health Service
OPCS	Office of Population Censuses and Surveys
PIS	Prescribing Information System
SIMD	Scottish Index of Multiple Deprivation
SMR01	Scottish Morbidity Record 01
TTR	time in therapeutic range
WHO	World Health Organization

meta-analysis of randomized controlled trials, DOACs were reported to be more effective compared with warfarin in preventing strokes or mortality.[9] It is not known whether the introduction of the DOACs has reduced disparities in treatment between women and men with AF.

In this study, we aimed to evaluate the trends in oral anticoagulation prescribing for women and men admitted to the hospital with nonvalvular AF and compare the factors influencing the prescription of vitamin K antagonist and DOACs.

METHODS

This study makes use of routine electronic health care data sources that are linked, deidentified, and held in the National Health Service (NHS) national safe haven, which is accessible by approved individuals who have undertaken the necessary governance training. Summary data can be made available on request to the corresponding author.

Study Design and Data Sources

We linked multiple national databases to conduct this nationwide cohort study. We identified all patients aged 18 years or older who were admitted to the hospital in Scotland with nonvalvular AF between January 1, 2010, and December 31, 2019, from the Scottish Morbidity Record (SMR01) held by Public Health Scotland. Individual patient episodes were linked to the national drug prescribing database held by the Prescribing Information System (PIS) and the General Register of Scotland (GRO), which contains information on all in-hospital and community deaths in the country.[10] Access to the data was approved by the Privacy Advisory Committee of the NHS Scotland Public Benefit and Privacy Panel for Health and Social Care and in accordance with the Declaration of Helsinki. As all data used in this analysis had already been collected and anonymized, individual patient consent was not required or sought.

Patient Population

Incident admissions to the hospital with AF were identified from hospital discharge records within the SMR01 database using codes from the *International Classification of Diseases, Tenth Revision* (*ICD-10*). We used the *ICD-10* code I48, which includes both AF and atrial flutter but does not include other forms of atrial arrhythmias. A 10-year look-back period was used to exclude any recurrent hospitalizations of the same individual patient (Data S1).[11] Patients with previous mitral valve surgery or on hemodialysis were excluded from this analysis because DOACs are currently contraindicated for these patients.

Definition of Covariates

Demographic information for each individual patient was obtained from the SMR01 database. We have

defined patients' sex as the self-reported sex documented in the SMR01 database. We used the Scottish Index of Multiple Deprivation (SIMD), an area-based measure of deprivation, to define socioeconomic status of each individual. The SIMD 2009 combines 31 indicators across 7 domains: income, employment, health, education, health, crime and housing, and access to services.[12] The overall SIMD is a weighted sum of the 7 domain scores across 6976 small areas (called data zones). These data zones are then ranked by SIMD quintile from most deprived (first quintile) to least deprived (fifth quintile).

Patient comorbidities were defined using information from previous hospitalizations, hospital procedures, and drug prescribing data. We categorized prescribed drugs using the World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC) classification system to define comorbid conditions. Using these comorbid conditions, we calculated each patient's CHA_2DS_2VASc score to define their individual risk of thromboembolic complications.[13] The full details on the hospital episode and ATC codes to define each comorbid condition are presented in Data S2. Using the same methodology, we calculated the Charlson Comorbidity Index (CCI) for each individual patient to assess burden of comorbidity. The CCI includes 19 conditions. Each condition is assigned a weight from 1 to 6 and summed to produce the score (range 1–37).

Outcomes

Bleeding Academic Research Consortium (BARC) (Data S3).[14] These codes have been validated using linked bespoke studies and electronic health records by the CALIBER group.[15]

Statistical Analysis

Baseline characteristics of women and men with incident hospitalization with nonvalvular AF were described. Categorical variables were described as proportions, while means and SDs were reported for continuous variables. We described trends in oral anticoagulation prescription for women and men hospitalized with incident nonvalvular AF between 2010 and 2019. In patients with thromboembolic risk factors (CHA_2DS_2VASc score >0 in men and >1 in women), we used a logistic regression model to evaluate the association between important patient factors such as age, sex, deprivation, burden of comorbidity, prior bleeding and thromboembolic risk, and prescription of oral anticoagulants. We initially performed these analyses for all oral anticoagulants and subsequently stratified by vitamin K antagonists and direct factor Xa inhibitors. We also constructed cumulative incidence functions to describe of women and men stratified by whether they were prescribed oral anticoagulation following the incident hospitalization with nonvalvular AF. We applied competing risk methodology to estimate the cumulative incidence function of ischemic stroke, MI, and bleeding to account for the competing risk of all-cause mortality.[16] All statistical analyses were performed in R version 3.6.1 (The R Foundation).

RESULTS

Overall, 172 989 patients had an incident hospitalization with nonvalvular AF in Scotland over the 10-year period between 2010 and 2019, of whom, 82 833 (48%) were women and 90 156 (52%) were men. Women presenting with nonvalvular AF were older than men (78±11 years versus 73±13 years) and had a higher CHA_2DS_2VASc score (4.1±1.3 versus 2.8±1.5). Compared with men, women had a similar prevalence of previous heart failure, hypertension, ischemic stroke, and prior bleeding, but a lower prevalence of diabetes and previous MI (Table).

Approximately half of all patients hospitalized with nonvalvular AF were prescribed oral anticoagulation therapy (51.3% [88 828/172 989]). The proportion of patients prescribed oral anticoagulation therapy increased from 36.2% in 2010 to 64.5% in 2019 (Figure 1). In patients with thromboembolic risk factors (CHA_2DS_2VASc score >0 in men and >1 in women), the proportion prescribed oral anticoagulation therapy was marginally higher (36.8% in 2010 and 66.3% in 2019) (Figure S1). Patients with thromboembolic risk factors who were not prescribed any oral anticoagulation therapy were of similar age (78±11 years versus 76±10 years) and had a similar CHA_2DS_2VASc score (3.6±1.4 versus 3.7±1.3) but were more likely to be women (51.8% versus 46.8%) compared with those who received oral anticoagulation therapy (Table S1). Throughout the study period, a lower proportion of women compared with men were prescribed oral anticoagulation (33% versus 41% in 2010 and 65% versus 68% in 2019) (Figure S2). In a multivariable logistic regression model adjusted for age, deprivation, comorbidity, prior bleeding, and CHA_2DS_2VASc score, women were significantly less likely to receive oral anticoagulation therapy compared with men (adjusted odds ratio [aOR], 0.68 [95% CI, 0.67–0.70]).

Of those with thromboembolic risk factors who were prescribed oral anticoagulation therapy, 53.5% (45 318/84 764) were prescribed vitamin K antagonists, while 45.5% (38 583/84 764) were prescribed direct factor Xa inhibitors and 1.0% (863/84 764) were prescribed direct thrombin inhibitors. Treatment with vitamin K antagonists declined from 100% of all oral anticoagulation therapy prescribed in 2010 to 15.9% in 2019 (Figure 1). Meanwhile, use of direct factor Xa inhibitors has increased from 0% to 83.6%. Direct thrombin

Table. Characteristics of Patients Hospitalized With AF Stratified by Sex

	Overall	Men	Women
No. of patients	172 989	90 156	82 833
Age, y	75.3 (12.1)	72.7 (12.5)	78.1 (11.1)
Previous medical conditions			
MI	7800 (4.5)	4646 (5.2)	3154 (3.8)
Stroke	3792 (2.2)	1824 (2.0)	1968 (2.4)
Heart failure	10 989 (6.4)	5941 (6.6)	5048 (6.1)
Previous coronary revascularization	7349 (4.2)	5411 (6.0)	1938 (2.3)
Hypertension	98 583 (57.0)	51 624 (57.3)	46 959 (56.7)
Chronic lower respiratory disease	39 335 (22.7)	19 175 (21.3)	20 160 (24.3)
Diabetes	23 803 (13.8)	14 016 (15.5)	9787 (11.8)
Previous bleeding	9599 (5.5)	5102 (5.7)	4497 (5.4)
CHA_2DS_2VASc score	3.4 (1.5)	2.8 (1.5)	4.1 (1.3)
SIMD quintile			
1 (most deprived)	34 224 (20.1)	16 927 (19.1)	17 297 (21.1)
2	37 183 (21.8)	18 538 (20.9)	18 645 (22.8)
3	35 326 (20.7)	18 583 (20.9)	16 743 (20.5)
4	33 569 (19.7)	18 267 (20.6)	15 302 (18.7)
5 (least deprived)	30 380 (17.8)	16 534 (18.6)	13 846 (16.9)
CCI			
0	113 722 (65.7)	59 032 (65.5)	54 690 (66.0)
1	36 964 (21.4)	18 899 (21.0)	18 065 (21.8)
2	15 116 (8.7)	8210 (9.1)	6906 (8.3)
≥3	7187 (4.2)	4015 (4.5)	3172 (3.8)

Values are presented as number (percentage). Scottish Index of Multiple Deprivation (SIMD) combines 31 indicators across 7 domains: income, employment, health, education, health, crime and housing, and access to services. The overall SIMD is ranked by SIMD quintile from most deprived (first quintile) to least deprived (fifth quintile). A higher Charlson Comorbidity Index (CCI) indicates greater comorbidity burden. AF indicates atrial fibrillation; and MI, myocardial infarction.

inhibitors peaked in 2013 at 1.7%, but this decreased to 0.6% in 2019. Throughout the study period, women were less likely to be prescribed vitamin K antagonists compared with men (33% versus 41% in 2010 and 9% versus 12% in 2019) (Figure 2A). Conversely, the proportion of women and men prescribed direct factor Xa inhibitors was similar (Figure 2B). In multivariable logistic regression modeling, women were significantly less likely to receive vitamin K antagonists compared with men (aOR, 0.68 [95% CI, 0.66–0.70]). Older patients and those with comorbidities were also less likely to receive vitamin K antagonists (aOR, 0.75 [95% CI, 0.74–0.76] per 10-year increments in age and aOR, 0.74 [95% CI, 0.73–0.74] per unit increase in CCI score, respectively) (Figure 3). These observations were consistent in an additional post hoc analysis adjusting for thromboembolic risk factors where sex category was removed from the CHA_2DS_2VASc score (Figure S3). There were fewer disparities in the prescription of direct factor Xa inhibitors (aOR for women versus men 0.92 [95% CI, 0.90–0.95]); however, those with a history of prior bleeding were less likely to receive direct factor Xa inhibitors (aOR, 0.69 [95% CI, 0.65–0.73]).

Patients not prescribed oral anticoagulation therapy were more likely to have subsequent MACE compared with those prescribed oral anticoagulation therapy at 30 days (14.9% [5914 of 39 608] versus 4.2% [1669 of 39 671] in women and 13.0% [4801 of 36 868] versus 4.4% [1970 of 45 093] in men) and 1 year (38.8% [15 380 of 39 608] versus 17.0% [6761 of 39 671] in women and 35.2% [12 977 of 36 868] versus 16.4% [7395 of 45 093] in men). (Table S2). Women who were not prescribed oral anticoagulation had the highest rates of subsequent ischemic stroke, all-cause mortality, and MACE compared with men who were or were not prescribed oral anticoagulation therapy, with no significant differences in incident major bleeding (Figure S4).

DISCUSSION

In this contemporary nationwide cohort study using individual patient data linkage, we evaluated the trends and factors associated with oral anticoagulation prescribing for women and men admitted to the hospital in Scotland with nonvalvular AF and their subsequent risk of all-cause mortality and bleeding over the past decade. We make several important observations. First, between 2010 and 2019, only half of all patients admitted with nonvalvular AF were prescribed any oral anticoagulation therapy, although this increased to nearly two-thirds by 2019. Women were less likely than men to receive oral anticoagulation therapy even after accounting for age, comorbidities, thromboembolic risk factors, and deprivation. Second, the disparity in oral anticoagulation therapy between women and men was attributable to vitamin K antagonists, while treatment with direct factor Xa inhibitors was similar between women and men. Treatment with factor Xa inhibitors was also associated with a reduction in treatment disparities in older patients and those with more comorbidities; however, those with prior bleeding were significantly less likely to receive this class of anticoagulant. Finally, women who were not treated with oral anticoagulation therapy experienced the highest rates of subsequent MACE and all-cause mortality with no significant difference in rates of bleeding.

Previous studies evaluating the association between sex and prescription of oral anticoagulation therapy have reported divergent findings. Several previous studies have reported similar rates of oral anticoagulation prescribing in women and men, while others have demonstrated that women were less likely to be prescribed oral anticoagulation.[17–20] Importantly, most

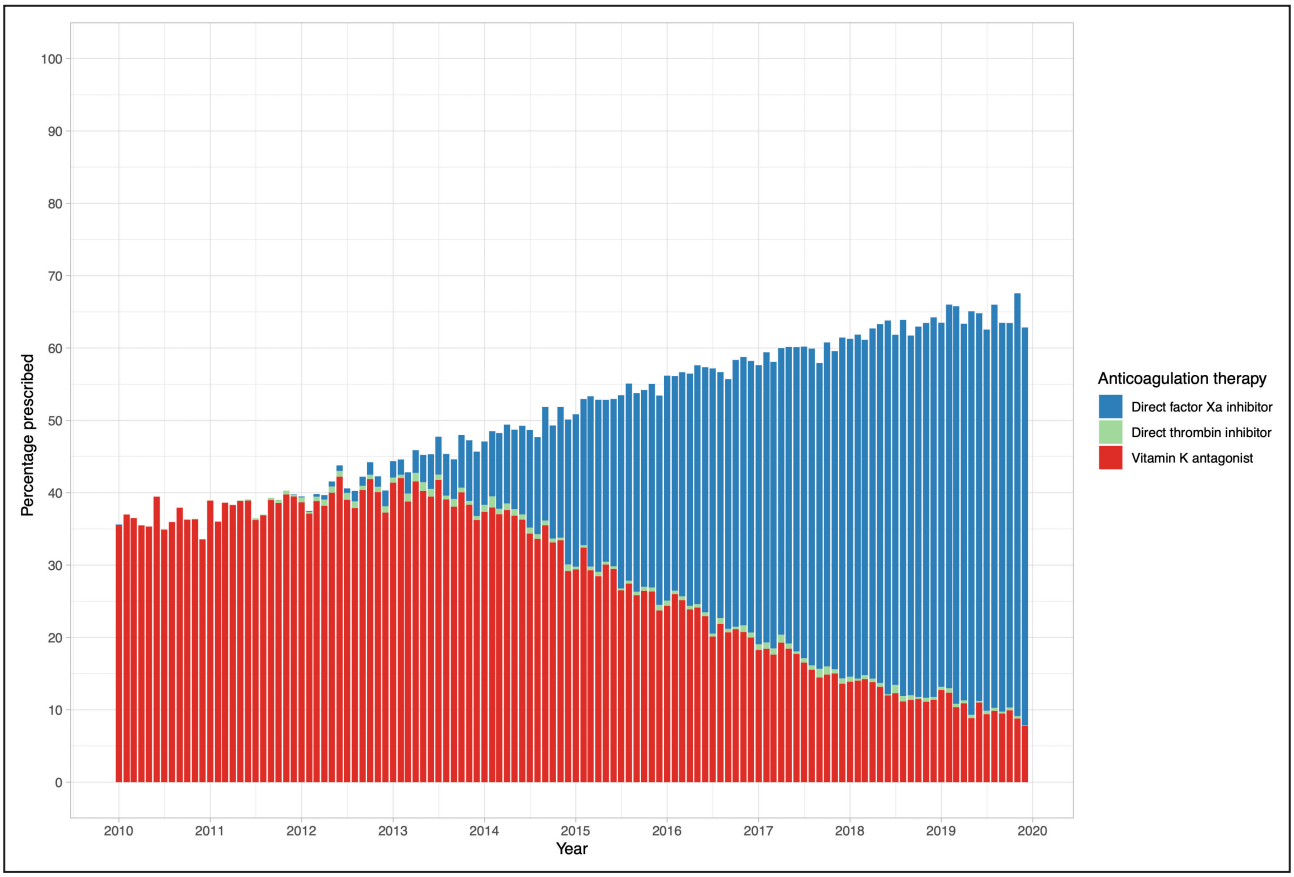

Figure 1. Trends in oral anticoagulation therapy for patients admitted to the hospital with nonvalvular atrial fibrillation in Scotland from 2010 to 2019.

of these data were derived from commercial insurance claims databases or patient registries that require individual patient consent and voluntary submission of data, which were likely to have introduced significant selection bias. In contrast, our study utilized a national database to identify all consecutive patients presenting to hospitals nationwide with incident AF without selection bias. Furthermore, most previous studies were conducted during the initial years after the introduction of DOACs into clinical practice when warfarin was the most widely prescribed oral anticoagulant. Here, we evaluated longer-term trends in oral anticoagulation therapy over a decade after introduction of DOACs and observed that trends in prescribing continued to evolve over time. Finally, previous studies have mainly identified patients in primary care or in outpatient settings, whereas we have included patients admitted to secondary care with incident AF. These patients are significantly older, frailer, and have more comorbidities and severe complications from AF and it is in this patient population where there may be more uncertainty about the risks and benefits of anticoagulation therapy.

Despite clear national[21] and international[1] guidelines highlighting female sex as an important thromboembolic risk factor, we observed that women remain less likely to receive oral anticoagulation therapy than men. In Scotland, all medications prescribed in primary and secondary care within the NHS is paid for by the government. Differences in oral anticoagulation prescribing between women and men persisted even after adjusting for age, deprivation, comorbidities, and CHA_2DS_2VASc score. Our analysis suggests that much of this disparity was primarily attributable to warfarin, while there was no difference in DOAC prescribing between women and men. Consistent with multiple other registries, we observed a rapid increase in prescription of direct factor Xa inhibitors for patients with AF in recent years, with a concurrent decrease in warfarin prescription.[22–24] Our data suggest that increased use of direct factor Xa inhibitors has, in effect, narrowed sex differences in oral anticoagulation prescribing in patients with AF over the past decade. It is therefore possible that if current trends in increased prescription of direct factor Xa inhibitor therapy continues, sex differences in oral anticoagulation therapy in patients with AF may be significantly reduced.

There are several reasons that may potentially explain sex differences in the prescription of warfarin and direct factor Xa inhibitors. Women may be more likely to decline warfarin therapy because of lack of social

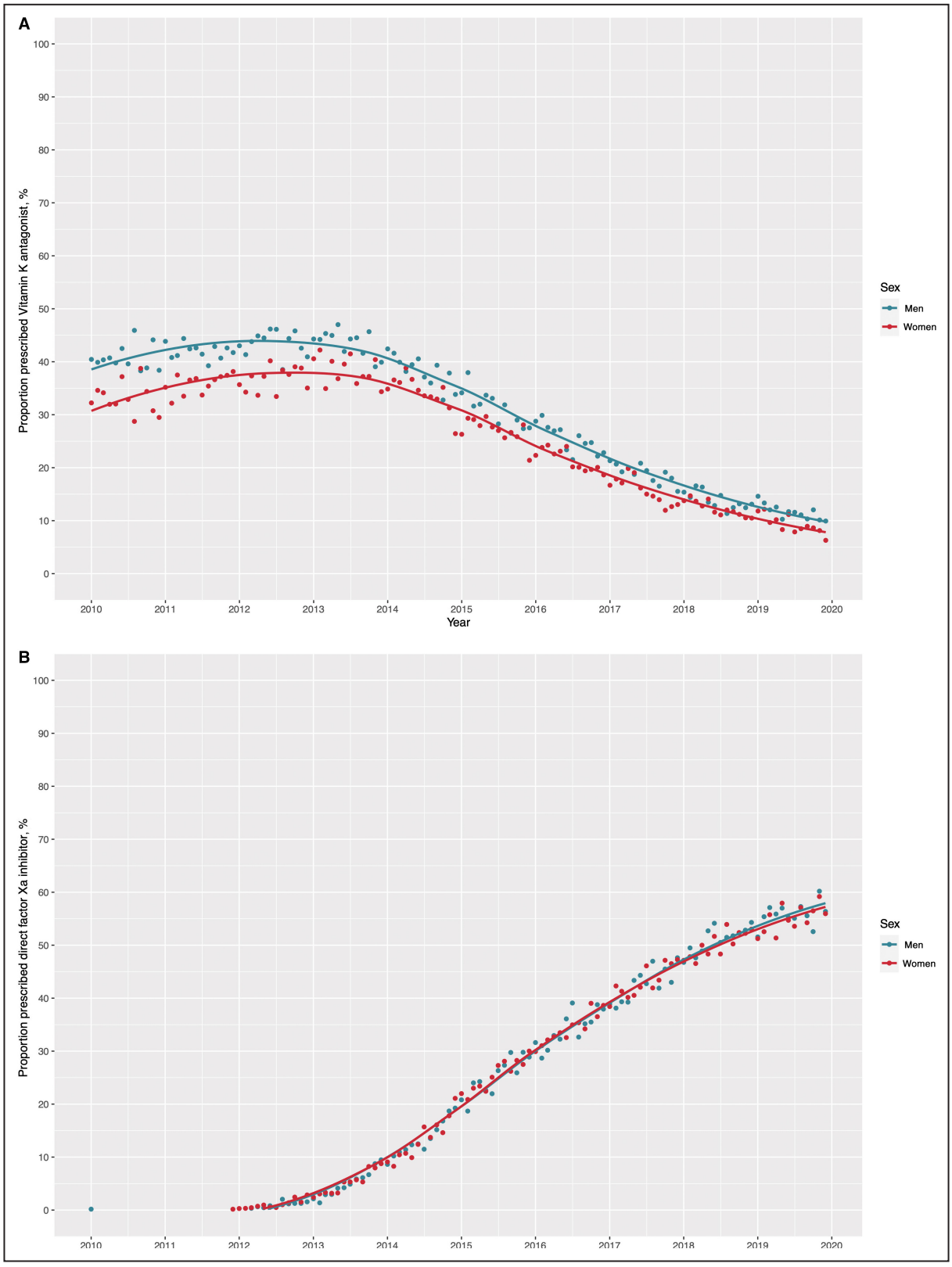

Figure 2. Trends in oral anticoagulation therapy for patients admitted to the hospital with nonvalvular atrial fibrillation in Scotland from 2010 to 2019 with thromboembolic risk factors (CHA_2DS_2VASc score >0 in men and >1 in women) stratified by sex.
A, Trends in vitamin K antagonist prescribing. **B**, Trends in factor Xa inhibitor prescribing.

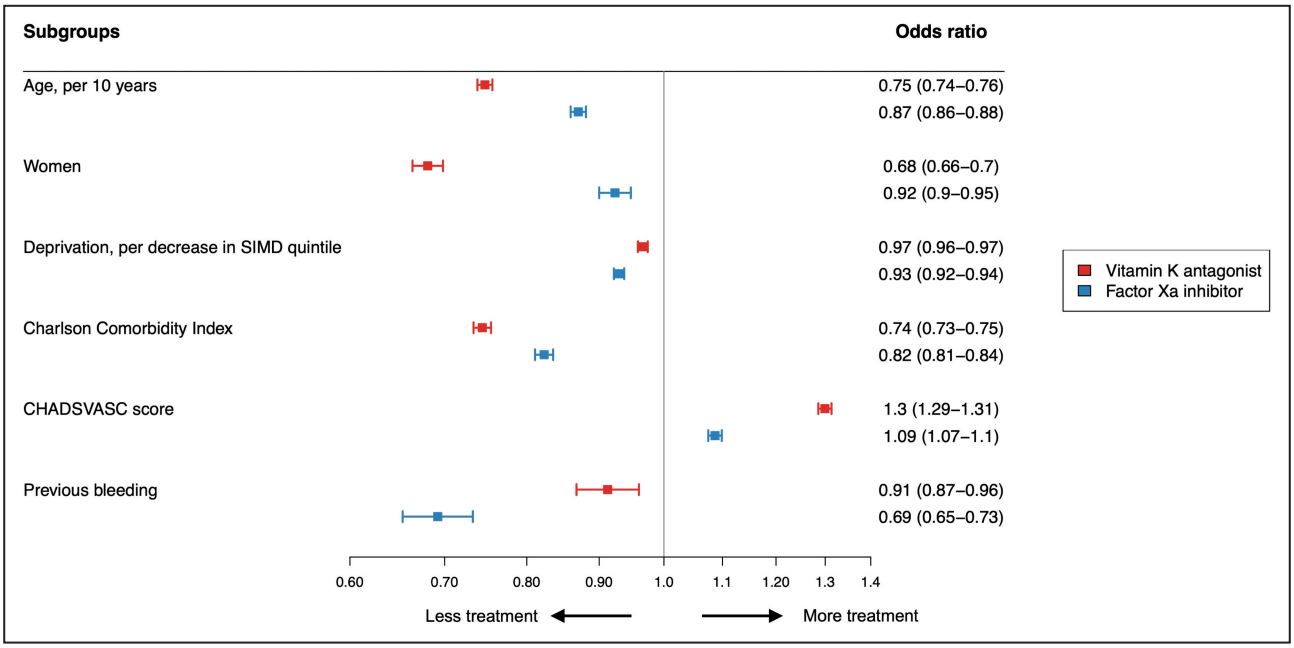

Figure 3. Factors associated with vitamin K antagonist and factor Xa inhibitor therapy in patients admitted to the hospital with nonvalvular atrial fibrillation with thromboembolic risk factors (CHA_2DS_2VASc score >0 in men and >1 in women). Odds ratios were derived from multivariable logistic regression models including age, sex, deprivation (Scottish Index of Multiple Deprivation [SIMD]), burden of comorbidity (Charlson Comorbidity Index), prior bleeding, and thromboembolic risk (CHA_2DS_2VASc score).

support or access to primary care to attend regular INR monitoring.[25] Indeed, multiple studies on patients treated with warfarin have reported significantly lower TTR in women compared with men.[26–29] Difficulty in achieving a stable INR may have also influenced clinicians' prescribing decisions since low TTR is strongly associated with reduced efficacy and increased risk of adverse outcomes such as bleeding.[30,31] In contrast to warfarin, factor Xa inhibitors have a predictable therapeutic effect without the need for regular INR monitoring. Furthermore, multiple studies have demonstrated greater benefit of factor Xa inhibitors in patients with labile INR.[32,33] This important advantage may have encouraged more women and their clinicians to pursue oral anticoagulation therapy with factor Xa inhibitors, in particular, those who may otherwise have decided not to receive warfarin therapy.

We acknowledge several limitations in this study. Despite optimal adjustment for potential confounders, it is possible that disparities in prescription of oral anticoagulation therapy in women and men were attributable to unmeasured sex-specific differences in baseline characteristics and we were unable to account for this residual confounding. Furthermore, we did not have access to detailed individual patient records; therefore, it is possible that a significant number of these patients had contraindications to anticoagulation therapy. However, it is unlikely that this is the case for most patients with nonvalvular AF in secondary care. While the prescribing database contains comprehensive data on all medications dispensed to individual patients, we do not have information on adherence to the medications. We also did not have information on individual patients' INR or TTR for patients taking warfarin. This may have introduced some exposure misclassification. Moreover, we did not have data on patients' sex. This may also be an important factor influencing prescribing decision-making and outcomes in addition to biological sex. Finally, we relied on *ICD* diagnostic codes to identify our study population and define comorbidities and subsequent outcomes. We accept that there may be a degree of inaccuracy in the coding of these events.

CONCLUSIONS

More than one-third of patients admitted to the hospital in Scotland with incident nonvalvular AF remained untreated with any oral anticoagulation. Women are significantly less likely to be prescribed oral anticoagulation therapy compared with men, and this is mainly attributable to vitamin K antagonists. Most patients admitted to the hospital in Scotland with incident nonvalvular AF are now treated with direct factor Xa inhibitors and this is associated with fewer treatment disparities between women and men and in older, more comorbid patients. If these trends continue, disparities in

oral anticoagulation prescribing between women and men with AF may be significantly reduced through increased treatment with factor Xa inhibitors.

ARTICLE INFORMATION

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Disclosures

A.C.Q., K.G.P., S.L., S.M., and B.S. are employees of Bristol Myers Squibb Pharmaceuticals Ltd. N.B. is an employee of Pfizer UK Ltd.

Supplemental Material

Data S1–S3
Tables S1–S2
Figures S1–S4

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SUPPLEMENTAL MATERIAL

Data S1. Method for calculating 10-year look back period.

Any hospitalization after the start of the cohort period, where there was no previous event within 10 years is considered incident and summed for each calendar year. The tables below show a worked example for the calculation of incident hospitalizations for two patients included in this study.

Example case 1:

Patient id	Episode id	Date	Diagnostic codes					Incident hospitalization
			Primary	Condition 1	Condition 2	Condition 3	Condition 4	
1	1	01/1994	427.3	410				0
1	2	01/2010	I21	I50	I48			1
1	3	01/2013	I48					0

Example case 2:

Patient id	Episode id	Date	Diagnostic codes					Incident hospitalization
			Primary	Condition 1	Condition 2	Condition 3	Condition 4	
2	1	01/2010	429	410	427.3			1
2	2	01/2013	427.3					0
2	3	01/2015	I48					0

Data S2. Hospital and Anatomical Therapeutic Chemical (ATC) Classification codes used to define patient comorbidity.

Comorbidity	Definition	
	ATC	ICD-10
Atrial fibrillation		I48
Myocardial infarction		I21, I22
Ischemic stroke		I63
Heart failure		I11.0, I13.0, I13.2, I42.6, I50
Hypertension	C02, C09, C08ca, C03a, C03ba11	
Chronic lower respiratory disease	R03	
Diabetes mellitus	A10	

Data S3. Bleeding Academic Research Consortium Definition for Bleeding (BARC) [14]

Types	Definition
Type 0	no bleeding
Type 1	bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a healthcare professional; may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a healthcare professional
Type 2	any overt, actionable sign of haemorrhage (eg, more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, 4, or 5 but does meet at least one of the following criteria: (1) requiring nonsurgical, medical intervention by a healthcare professional, (2) leading to hospitalization or increased level of care, or (3) prompting evaluation
Type 3a	Overt bleeding plus haemoglobin drop of 3 to <5 g/dL (provided haemoglobin drop is related to bleed) or any transfusion with overt bleeding
Type 3b	Overt bleeding plus haemoglobin drop ≥5 g/dL (provided haemoglobin drop is related to bleed), cardiac tamponade, bleeding requiring surgical intervention for control (excluding dental/nasal/skin/haemorrhoid), or bleeding requiring intravenous vasoactive agents
Type 3c	Intracranial haemorrhage (does not include micro bleeds or haemorrhagic transformation, does include intraspinal), subcategories confirmed by autopsy or imaging or lumbar puncture, or intraocular bleed compromising vision
Type 4	CABG-related bleeding defined as perioperative intracranial bleeding within 48 hr, reoperation after closure of sternotomy for the purpose of controlling bleeding, transfusion of ≥5 U whole blood or packed red blood cells within a 48-h period, or chest tube output ≥2L within a 24-h period

Type 5a	Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious
Type 5b	Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation

Diagnostic codes to define bleeding events according to the Consensus Report from the Bleeding Academic Research Consortium (BARC) criteria.
(1) BARC 2 **(2)** BARC 3a **(3)** BARC 3b **(4)** BARC 3b or 4 if after CABG **(5)** BARC 3c
(6) BARC 3c or 4 if after CABG **(7)** BARC 4 **(8)** BARC 5

ICD code	ICD definition	category
K226	Gastro-oesophageal laceration-haemorrhage syndrome	1
K625	Haemorrhage of anus and rectum	1
K920	Haematemesis	1
K921	Melaena	1
K922	Gastrointestinal haemorrhage, unspecified	1
N837	Haematoma of broad ligament	1
N938	Other specified abnormal uterine and vaginal bleeding	1
N939	Abnormal uterine and vaginal bleeding, unspecified	1
O031	Spontaneous abortion ; Incomplete, complicated by delayed or excessive haemorrhage	1
O036	Spontaneous abortion; Complete or unspecified, complicated by excessive haemorrhage	1
O041	Medical abortion ; Incomplete, complicated by delayed or excessive haemorrhage	1
O046	Medical abortion ; Complete or unspecified, complicated by delayed or excessive haemorrhage	1
O051	Other abortion ; Incomplete, complicated by delayed or excessive haemorrhage	1
O056	Other abortion ; Complete or unspecified, complicated by delayed or excessive haemorrhage	1
O061	Unspecified abortion ; Incomplete, complicated by delayed or excessive haemorrhage	1
O066	Unspecified abortion ; Complete or unspecified, complicated by excessive haemorrhage	1
O071	Failed medical abortion, complicated by delayed or excessive haemorrhage	1
O076	Other and unspecified failed attempted abortion, complicated by excessive haemorrhage	1
O081	Delayed or excessive haemorrhage following abortion and ectopic and molar pregnancy	1
O208	Other haemorrhage in early pregnancy	1
O209	Haemorrhage in early pregnancy, unspecified	1

O46	Antepartum haemorrhage, not elsewhere classified	1
O717	Obstetric haematoma of pelvis	1
O902	Haematoma of obstetric wound	1
R042	Haemoptysis	1
T810	Haemorrhage and haematoma complicating a procedure, not elsewhere classified	1
K250	Gastric ulcer ; Acute with haemorrhage	2
K254	Gastric ulcer ; Chronic or unspecified with haemorrhage	2
K260	Duodenal ulcer ; Acute with haemorrhage	2
K264	Duodenal ulcer ; Chronic or unspecified with haemorrhage	2
K270	Peptic ulcer, site unspecified ; Acute with haemorrhage	2
K274	Peptic ulcer, site unspecified ; Chronic or unspecified with haemorrhage	2
K280	Gastrojejunal ulcer ; Acute with haemorrhage	2
K284	Gastrojejunal ulcer ; Chronic or unspecified with haemorrhage	2
K290	Acute haemorrhagic gastritis	2
O67	Labour and delivery complicated by intrapartum haemorrhage, not elsewhere classified	2
O720	Third-stage haemorrhage	2
O721	Other immediate postpartum haemorrhage	2
O722	Delayed and secondary postpartum haemorrhage	2
P261	Massive pulmonary haemorrhage originating in the perinatal period	2
R041	Haemorrhage from throat	2
R048	Haemorrhage from other sites in respiratory passages	2
R049	Haemorrhage from respiratory passages, unspecified	2
I850	Oesophageal varices with bleeding	3
K252	Gastric ulcer ; Acute with both haemorrhage and perforation	3
K256	Gastric ulcer ; Chronic or unspecified with both haemorrhage and perforation	3
K262	Duodenal ulcer ; Acute with both haemorrhage and perforation	3
K266	Duodenal ulcer ; Chronic or unspecified with both haemorrhage and perforation	3
K272	Peptic ulcer, site unspecified ; Acute with both haemorrhage and perforation	3
K276	Peptic ulcer, site unspecified ; Chronic or unspecified with both haemorrhage and perforation	3
K282	Gastrojejunal ulcer ; Acute with both haemorrhage and perforation	3
K286	Gastrojejunal ulcer ; Chronic or unspecified with both haemorrhage and perforation	3
H356	Retinal haemorrhage	5
H431	Vitreous haemorrhage	5
H450	Vitreous haemorrhage in diseases classified elsewhere	5
I60	Subarachnoid haemorrhage	5
I61	Intracerebral haemorrhage	5
I62	Other nontraumatic intracranial haemorrhage	5
I690	Sequelae of subarachnoid haemorrhage	5

I692	Sequelae of other nontraumatic intracranial haemorrhage	5
S064	Epidural haemorrhage	5
S065	Traumatic subdural haemorrhage	5
S066	Traumatic subarachnoid haemorrhage	5
I230	Haemopericardium as current complication following acute myocardial infarction	7
I312	Haemopericardium, not elsewhere classified	7

Table S1. Characteristics of patients hospitalized with atrial fibrillation with thromboembolic risk factors (CHA_2DS_2VASc score >0 in men and >1 in women) stratified by prescription of oral anticoagulation

	Overall	Prescribed anticoagulation	No anticoagulation
Number of patients	161240	84764	76476
Age, years	76.9 (10.5)	75.8 (9.9)	78.2 (11.0)
Women	79279 (49.2)	39671 (46.8)	39608 (51.8)
Previous medical conditions			
Myocardial infarction	7645 (4.7)	2971 (3.5)	4674 (6.1)
Stroke	3792 (2.4)	1960 (2.3)	1832 (2.4)
Heart Failure	10989 (6.8)	5069 (6.0)	5920 (7.7)
Previous coronary revascularisation	7205 (4.5)	2814 (3.3)	4391 (5.7)
Hypertension	98583 (61.1)	56134 (66.2)	42449 (55.5)
Chronic lower respiratory disease	37335 (23.2)	19291 (22.8)	18044 (23.6)
Diabetes mellitus	23803 (14.8)	13287 (15.7)	10516 (13.8)
Previous bleeding	9152 (5.7)	3751 (4.4)	5401 (7.1)
CHA_2DS_2VASc score	3.7 (1.3)	3.7 (1.3)	3.6 (1.4)
SIMD quintile			
1 (most deprived)	31701 (19.9)	15388 (18.3)	16313 (21.7)
2	34849 (21.9)	17736 (21.1)	17113 (22.8)
3	33024 (20.7)	17568 (20.9)	15456 (20.6)
4	31389 (19.7)	17550 (20.8)	13839 (18.4)
5 (least deprived)	28414 (17.8)	16009 (19.0)	12405 (16.5)
Charlson Comorbidity Index			
0	103940 (64.5)	60035 (70.8)	43905 (57.4)
1	35372 (21.9)	15868 (18.7)	19504 (25.5)
2	14779 (9.2)	6118 (7.2)	8661 (11.3)
≥3	7149 (4.4)	2743 (3.2)	4406 (5.8)

Presented as number of patients (%). Abbreviations: SIMD = Scottish index for multiple deprivation. SIMD combines 31 indicators across 7 domains: income, employment, health, education, health, crime and housing, and access to services. The overall SIMD index are ranked by SIMD quintile from most deprived (1st quintile) to least deprived (5th quintile). A higher Charlson Comorbidity index indicates greater comorbidity burden.

Table S2. Outcomes of patients hospitalized with atrial fibrillation with thromboembolic risk factors (CHA_2DS_2VASc score >0 in men and >1 in women) stratified by sex and prescription of oral anticoagulation

	Overall	Men		Women	
		Prescribed anticoagulation	No anticoagulation	Prescribed anticoagulation	No anticoagulation
Number of patients	161240	45093	36868	39671	39608
Events at 30 days					
Myocardial infarction	6846 (4.2)	1519 (3.4)	2373 (6.4)	954 (2.4)	2000 (5.0)
Ischemic stroke	6107 (3.8)	1637 (3.6)	1136 (3.1)	1635 (4.1)	1699 (4.3)
Major bleeding	3329 (2.1)	858 (1.9)	974 (2.6)	587 (1.5)	910 (2.3)
Cardiac death	5328 (3.3)	655 (1.5)	1753 (4.8)	606 (1.5)	2314 (5.8)
All-cause death	12148 (7.5)	1321 (2.9)	4253 (11.5)	1139 (2.9)	5435 (13.7)
MACE	14354 (8.9)	1970 (4.4)	4801 (13.0)	1669 (4.2)	5914 (14.9)
Events at 1 year					
Myocardial infarction	10165 (6.3)	2444 (5.4)	3268 (8.9)	1612 (4.1)	2841 (7.2)
Ischemic stroke	9936 (6.2)	2323 (5.2)	2035 (5.5)	2470 (6.2)	3108 (7.8)
Major bleeding	7524 (4.7)	2116 (4.7)	1935 (5.2)	1732 (4.4)	1741 (4.4)
Cardiac death	16146 (10.0)	2979 (6.6)	4368 (11.8)	2916 (7.4)	5883 (14.9)
All-cause death	38213 (23.7)	6135 (13.6)	11950 (32.4)	5723 (14.4)	14405 (36.4)
MACE	42513 (26.4)	7395 (16.4)	12977 (35.2)	6761 (17.0)	15380 (38.8)

Figure S1. Trends in oral anticoagulation therapy for patients admitted to hospital with non-valvular atrial fibrillation with thromboembolic risk factors (CHA_2DS_2VASc score >0 in men and >1 in women)

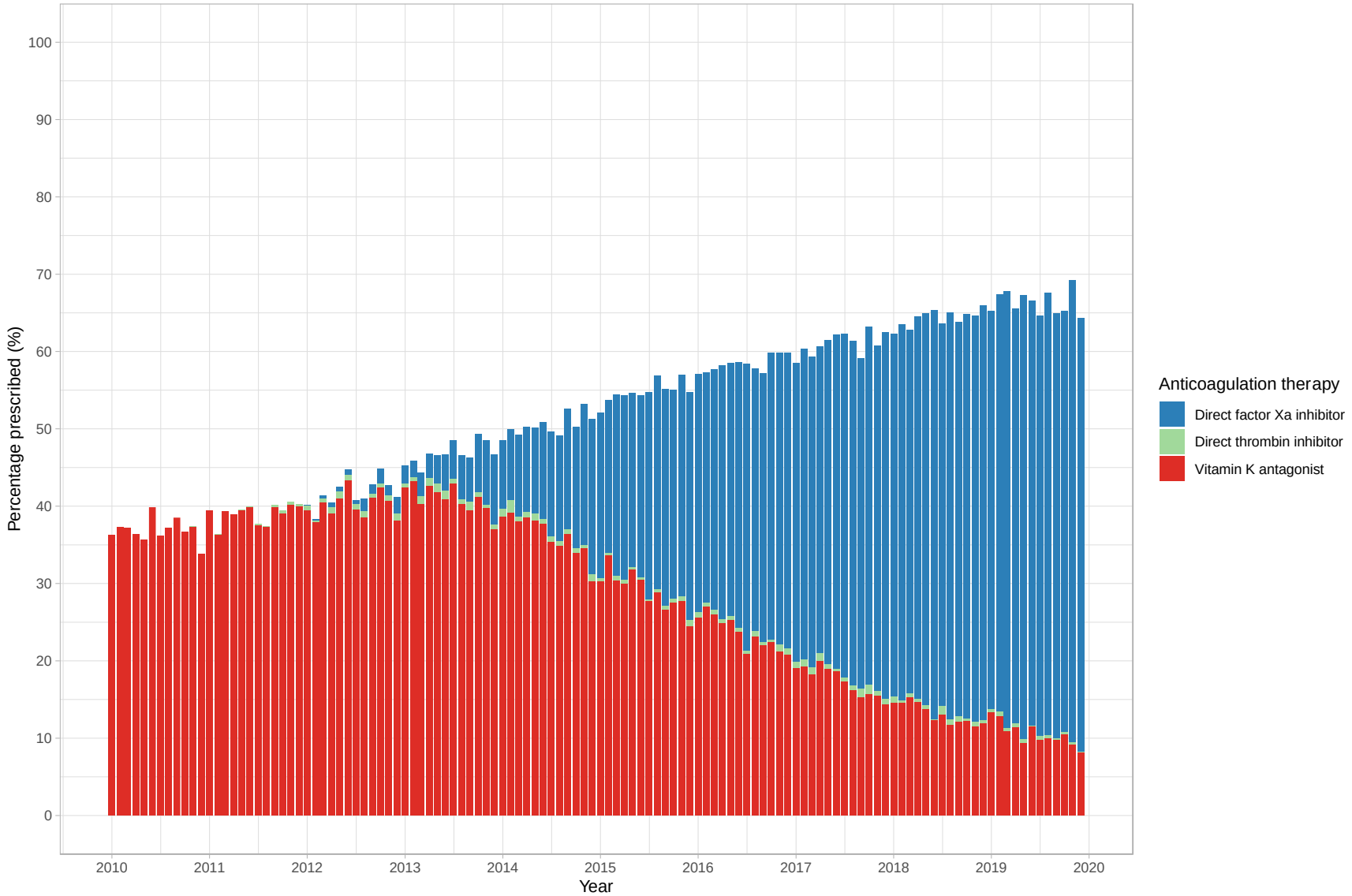

Figure S2. Trends in oral anticoagulation therapy for patients admitted to hospital with non-valvular atrial fibrillation with thromboembolic risk factors (CHA_2DS_2VASc score >0 in men and >1 in women) stratified by sex

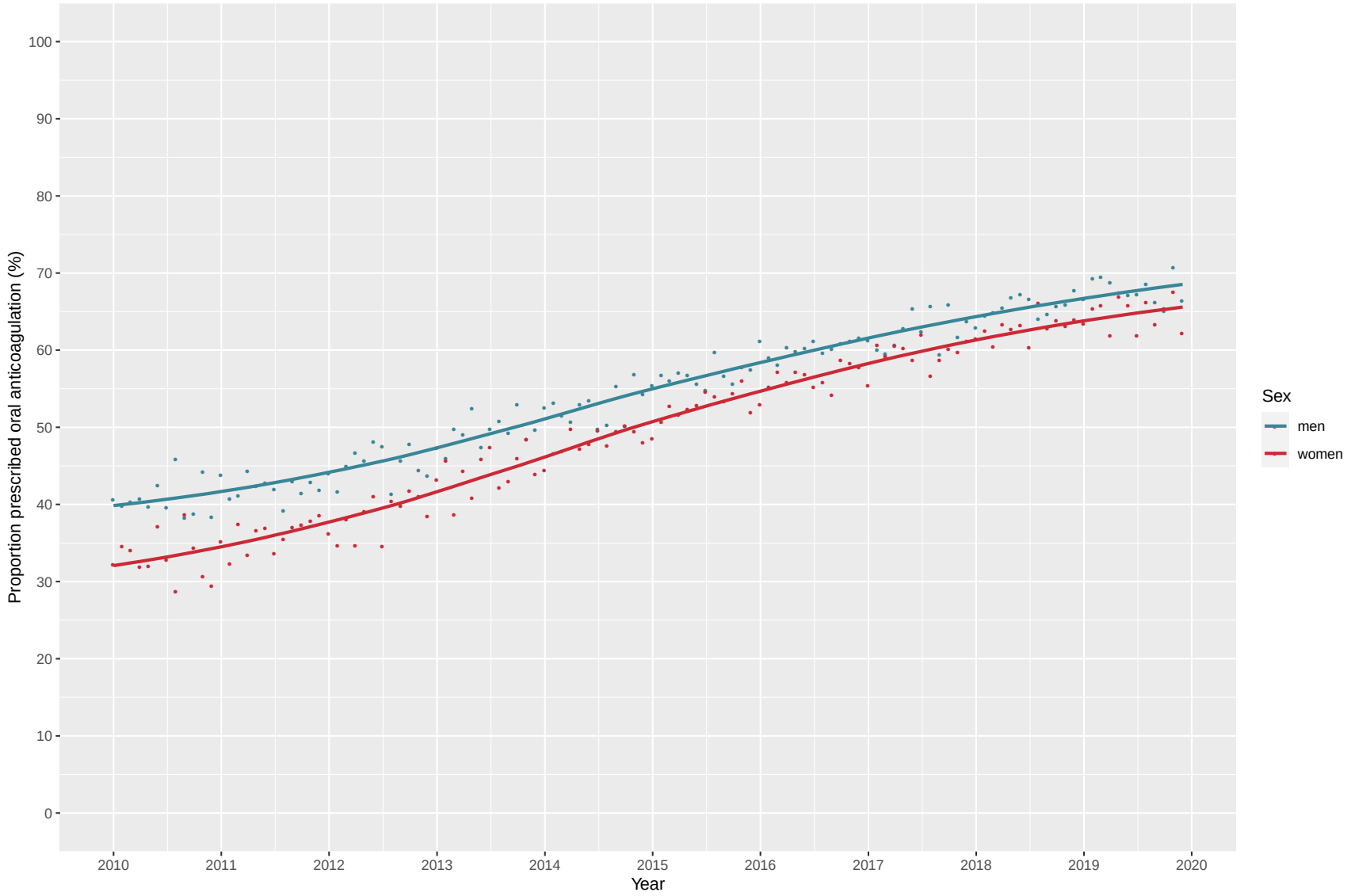

Figure S3. Factors associated with vitamin K antagonist and factor Xa inhibitor therapy in patients admitted to hospital with non-valvular atrial fibrillation with thromboembolic risk factors (CHA2DS2VASc score >0 in men and >1 in women).

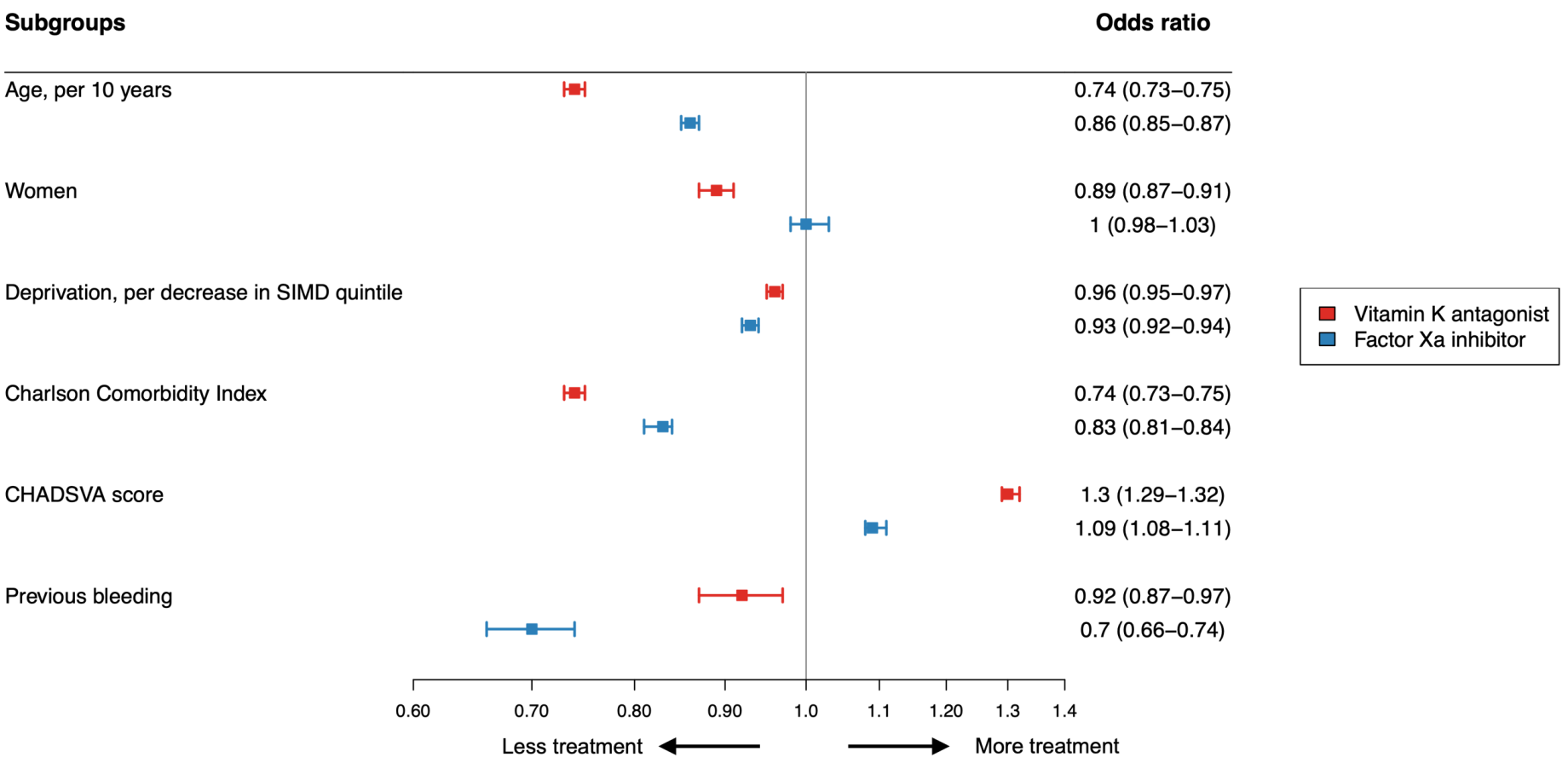

Figure S4. Cumulative incidence functions of outcomes of patients admitted to hospital with non-valvular atrial fibrillation with thromboembolic risk factors (CHA_2DS_2VASc score >0 in men and >1 in women) stratified by sex and prescription of oral anticoagulation therapy