Teppo, Konsta; Airaksinen, K. E.Juhani; Jaakkola, Jussi; Halminen, Olli; Salmela, Birgitta; Kalatsova, Ksenia; Kouki, Elis; Haukka, Jari; Putaala, Jukka; Linna, Miika; Aro, Aapo L.; Mustonen, Pirjo; Hartikainen, Juha; Lehto, Mika

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Published in:
European Journal of Clinical Investigation

DOI:
10.1111/eci.14107

Published: 01/01/2024

Document Version
Publisher's PDF, also known as Version of record

Received: 31 August 2023 | Accepted: 5 October 2023

DOI: 10.1111/eci.14107

ORIGINAL ARTICLE

WILEY

Temporal trends of gender disparities in oral anticoagulant use in patients with atrial fibrillation

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Funding information
Aarne Koskelon Säätiö, Grant/Award Number: N/A; Helsingin ja Uudenmaan Sairaanhoitopiiri; Sydäntutkimussäätiö

Abstract

Aims: To investigate sex-specific temporal trends in the initiation of oral anticoagulant (OAC) therapy among patients diagnosed with atrial fibrillation (AF) in Finland between 2007 and 2018.

Methods: The registry-linkage Finnish AntiCoagulation in Atrial Fibrillation (FinACAF) Study included all patients with incident AF in Finland from 2007 to 2018. The primary outcome was the initiation of any OAC therapy.

Results: We identified 229,565 patients with new-onset AF (50.0% women; mean age 72.7 years). The initiation of OAC therapy increased continuously during the observation period. While women were more likely to receive OAC therapy overall, after adjusting for age, stroke risk factors and other confounding factors, female sex was associated with a marginally lower initiation of OACs (unadjusted and adjusted hazard ratios comparing women to men: 1.08 (1.07–1.10) and 0.97 (0.96–0.98), respectively). Importantly, the gender disparities in OAC use attenuated and reached parity by the end of the observation period. Furthermore, when only patients eligible for OAC therapy according to the contemporary guidelines were included in the analyses, the gender inequalities in OAC initiation appeared

minimal. Implementation of direct OACs for stroke prevention was slightly slower among women.

Conclusion: This nationwide retrospective cohort study covering all patients with incident AF in Finland from 2007 to 2018 observed that although female sex was initially associated with a lower initiation of OAC therapy, the sex-related disparities resolved over the course of the study period.

KEYWORDS

atrial fibrillation, gender disparities, oral anticoagulant therapy, stroke prevention, temporal trends

1 | INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia, affecting up to 5.2% of the adult population.[1] It represents a major cause of ischemic stroke and is in addition associated with dementia, hospitalizations and higher mortality.[2,3] Fortunately, oral anticoagulant (OAC) therapy can effectively mitigate the risk of stroke and death in patients with AF at risk of stroke. Despite the well-established benefits of OAC therapy, its underuse in patients with AF is common, and profound disparities in stroke prevention have been reported among patient groups defined by characteristics such as age, race, socioeconomic status and mental health conditions.[4–12]

A higher risk of ischemic stroke in women compared to men was evident in the early OAC trials and has been later confirmed in observational studies.[13,14] Therefore, in 2010, female sex was incorporated into the CHA_2DS_2-VASc stroke risk score, which was subsequently adopted to the guidelines on AF management and became widely used in clinical practice.[15–17] Thereafter, a growing body of evidence elucidated that female sex functions more as a risk modifier rather than as an independent risk factor, resulting in updates to the guidelines on OAC therapy in 2016, recommending OAC therapy for women with CHA2DS2-VASc score ≥3 instead of ≥2.[18–20]

Sex-related disparities have been reported in the management and prognosis of several medical conditions.[21–24] Likewise, there are reports of lower use of OAC therapy among women compared to men in patients with AF.[4] While the use of stroke prevention in patients with AF has increased substantially during the past two decades, there is a paucity of information on sex-specific temporal trends in the use of OAC therapy, and how the incorporation of female sex in the stroke risk scores and the updates in the guidelines have translated into clinical practice of stroke prevention in men and women.[25] Therefore, we conducted a nationwide cohort study covering all patients with incident AF in Finland to explore the developments in the initiation of OAC therapy among men and women between 2007 and 2018.

2 | METHODS

2.1 | Study population

The Finnish AntiCoagulation in Atrial Fibrillation (FinACAF) Study (ClinicalTrials Identifier: NCT04645537; ENCePP Identifier: EUPAS29845) is a nationwide retrospective cohort study that includes all patients documented with AF in Finland from 2004 to 2018.[26] Patients were identified using all available national healthcare registers, including hospitalizations and outpatient specialist visits (HILMO), primary healthcare (AvoHILMO), and the National Reimbursement Register maintained by the Social Insurance Institute (KELA). The cohort inclusion criterion was an International Classification of Diseases, Tenth Revision (ICD-10) diagnosis code of I48, encompassing AF and atrial flutter, collectively referred to as AF, recorded between 2004 and 2018. Exclusion criteria encompassed permanent emigration abroad before 31 December 2018, and age below 20 years at AF diagnosis. The present sub-study was conducted within a cohort of patients with incident AF from 2007 to 2018, established in previous studies of the FinACAF cohort.[25,27,28] Follow-up started from the initial AF diagnosis and continued until the initiation of OAC therapy, death or 31 December 2018, whichever came first.

The management of AF evolved considerably during our study period. The European Society of Cardiology (ESC) published guidelines revising the recommendations on OAC therapy at the end of August in both 2010 and in 2016.[17,18] To account for these changes, and to conduct a focused examination of potential disparities in the real-world adoption of clinical practice guidelines, we selected a subset of patients who were recommended to receive OAC therapy across the study period, considering the

guidelines effective from 1 September in 2010 and 2016. In other words, we considered OAC therapy to be recommended for patients with baseline $CHADS_2$ score ≥2 until 1 September 2010, followed by CHA_2DS_2-VASc score ≥2 until 1 September 2016, and thereafter, CHA_2DS_2-VASc score ≥2 for men and CHA_2DS_2-VASc score ≥3 for women.

Data on baseline comorbidities were obtained from the aforementioned healthcare registers. The process of cohort construction is summarized in Figure S1, and the definitions of baseline comorbidities are presented in Table S1.

2.2 | Initiation of OAC

The primary outcome was the initiation of OAC therapy, which was considered to occur on the date of the first fulfilled OAC (warfarin, apixaban, dabigatran, edoxaban or rivaroxaban) prescription after the cohort entry. The data on fulfilled prescriptions were obtained from nationwide data covering all pharmacy purchases.

2.3 | Study ethics

The study protocol was approved by the Ethics Committee of the Medical Faculty of Helsinki University, Helsinki, Finland (nr. 15/2017) and received research permission from the Helsinki University Hospital (HUS/46/2018). Respective permissions were obtained from the Finnish register holders (KELA 138/522/2018; THL 2101/5.05.00/2018; Population Register Centre VRK/1291/2019-3; Statistics Finland TK-53-1713-18 / u1281; and Tax Register VH/874/07.01.03/2019). Patients' personal identification numbers were pseudonymized, and the research group received individualized but unidentifiable data. Informed consent was waived due to the retrospective registry nature of the study. The study conforms to the Declaration of Helsinki as revised in 2013.

2.4 | Statistical analyses

We calculated unadjusted and adjusted hazard ratios (HRs) with 95% confidence intervals for the initiation of OAC therapy in the overall cohort, as well as in the subset of OAC eligible patients, with the cause-specific Cox hazards regression with all-cause death treated as a competing event. The visual assessment of the log-negative log survival curves indicated that the proportional hazards assumption was met. Adjusted HRs were computed in two consecutive models, with the Model 1 including calendar year of AF diagnosis and factors of the CHA_2DS_2-VASc score (age as a categorical variable in 10-year intervals, hypertension, diabetes, heart failure, prior ischemic stroke or transient ischemic attack and vascular disease). The Model 2 included additionally the following variables: prior bleeding, alcohol use disorder, renal failure, liver cirrhosis or failure, cancer, dementia, psychiatric disorders and income level (divided into tertiles). Furthermore, we generated Kaplan–Meier curves to depict the cumulative incidence of OAC initiation.

Subsequently, the regression was fitted with an interaction term between the year of AF diagnosis and sex to assess whether the association of sex and OAC initiation changes according to the cohort entry year. As a significant interaction was observed, annual unadjusted and adjusted HRs were computed in the overall cohort, as well as in the subset of patients eligible for OAC therapy according to the contemporary guidelines. The adjusted analyses for annual HRs included the variables of the abovementioned Model 2. Additionally, we assessed the proportion of men and women initiating OAC therapy within the first year after AF diagnosis (patients diagnosed with AF in 2018 were excluded in this analysis, since they had less than 1 year of follow-up).

Moreover, unadjusted and adjusted odds ratios for initiating OAC therapy with direct oral anticoagulant (DOAC) were computed using binary logistic regression, including only patients who initiated OAC therapy during the follow-up period. The adjusted analyses in the binary logistic regression included the same variables as the abovementioned Model 2 with Cox regression. Baseline variables were compared using the Chi-squared test and Student's *t*-test. Statistical analyses were conducted using IBM SPSS Statistics software version 28.0 (SPSS, Inc.) and R version 4.0.5 (R Core Team, Vienna, Austria; https://www.R-project.org).

3 | RESULTS

We identified 229,565 patients with new-onset AF (50.0% women; mean age 72.7 years; mean follow-up time 1.4 years). When compared to men, women were older, had a higher risk of stroke, lower income and less frequently history of alcohol abuse or bleeding events (Table 1). According to the contemporary guidelines on AF management, the proportion of patients recommended to receive OAC therapy was consistently higher in women across the study period. The proportion of OAC eligible patients increased considerably after the 2010 ESC guidelines for both men and women, with the proportion in women reaching as high as 96.2% in 2015, followed by a decrease in women after the 2016 ESC guideline to the level of 87.1% (Figure 1).

TABLE 1 Baseline characteristics of the study cohort.

	Women	Men	
	n = 114,823	*n* = 114,747	*p*-value
Mean age, years	76.6 (11.8)	68.9 (13.4)	<0.001
Income quartiles			<0.001
First (lowest)	46.0	22.1	
Second	33.2	31.8	
Third (highest)	20.7	46.1	
Comorbidities			
Any vascular disease	27.0	29.1	<0.001
Diabetes	20.7	22.5	<0.001
Dyslipidemia	49.1	46.5	<0.001
Heart failure	19.3	15.4	<0.001
Hypertension	80.4	67.9	<0.001
Prior IS or TIA	16.8	14.0	<0.001
Abnormal liver function	0.4	0.6	<0.001
Abnormal renal function	3.6	4.4	<0.001
Alcohol use disorder	1.6	6.3	<0.001
Cancer	22.1	19.1	<0.001
Dementia	6.7	3.6	<0.001
Prior bleeding	9.1	12.3	<0.001
Psychiatric disorder	13.4	13.6	0.05
Risk scores			
Mean modified HAS-BLED score	2.6 (0.9)	2.4 (1.1)	<0.001
Mean CHA_2DS_2-VASc score	4.2 (1.6)	2.6 (1.8)	<0.001
Stroke risk categories			<0.001
Low stroke risk	4.3	12.4	
Moderate stroke risk	10.7	17.7	
High stroke risk	85.0	70.0	

Note: Values denote proportions (%) or mean (standard deviation). Abbreviations: CHA_2DS_2-VASc score, congestive heart failure (1 point), hypertension (1 point), age ≥ 75 years (2 points), diabetes (1 point), history of stroke or TIA (2 points), vascular disease (1 point), age 65–74 years (1 point), sex category (female) (1 point); IS, ischemic stroke; modified HAS-BLED score, hypertension (1 point), abnormal renal or liver function (1 point each), prior stroke (1 point), bleeding history (1 point), age > 65 years (1 point), alcohol abuse (1 point), concomitant antiplatelet/NSAIDs (1 point) (no labile INR, max score 8); TIA, transient ischemic attack. Stroke risk categories based on CHA_2DS_2-VASc score: low 0 in men and 0–1 in women; moderate 1 in men and 2 in women; high >1 in men and >2 in women.

The crude proportion of patients initiating OACs within the first year after AF diagnosis increased continuously during the observation period in both men and women (2007–2017: from 44.4% to 74.6% in men and from 42.9% to 78.1% in women). In the overall cohort, among patients under 65 years at the diagnosis of AF, women were less likely than men to start OAC therapy within the first year after AF diagnosis throughout the observation period. Among patients aged 65–74 years, women were marginally less likely to initiate OACs compared to men until 2012, and thereafter, women exhibited a higher likelihood of OAC initiation. Among patients aged 75 years or more, the crude gender disparities in OAC initiation within 1-year follow-up were minimal (Figure S2). Among the subset of patients eligible for OAC therapy, women were initially less likely to start OACs, but the disparities attenuated over the course of the study period (Figure 2). Women were also slightly less likely to initiate OAC therapy with DOAC throughout the study period both in the unadjusted and adjusted analyses (adjusted odds ratio with 95% confidence interval 0.96 [0.93–0.99]; Figure S3, Table S2).

During the whole observation period, in the overall cohort, women were more likely to receive OAC therapy

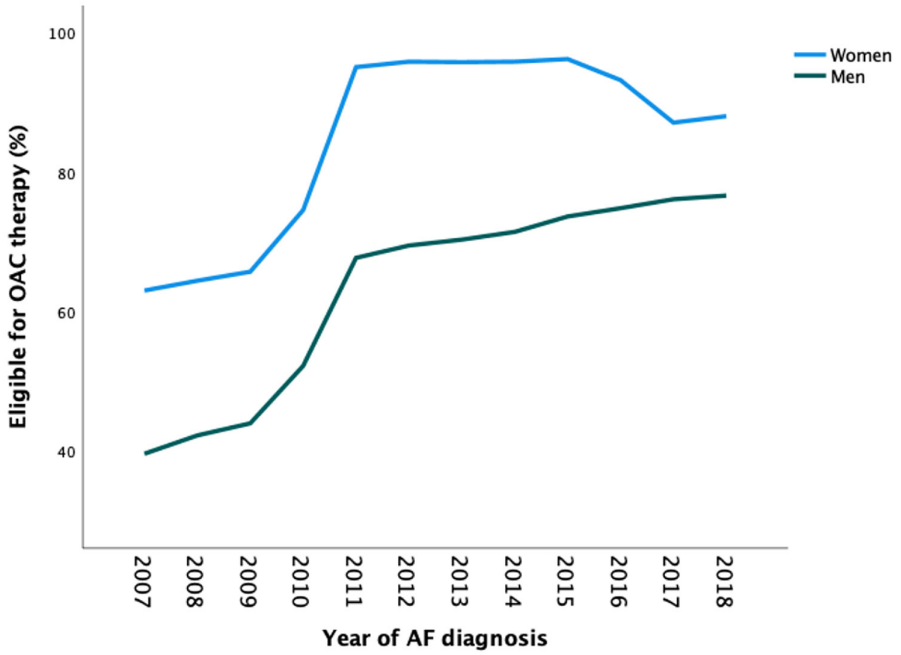

FIGURE 1 Trends in the proportion of patients eligible for OAC therapy according to the contemporary guidelines ($CHADS_2$ score ≥2 until 1 September 2010, followed by CHA_2DS_2-VASc score ≥2 until 1 September 2016, and thereafter CHA_2DS_2-VASc score ≥2 for men and CHA_2DS_2-VASc score ≥3 for women).

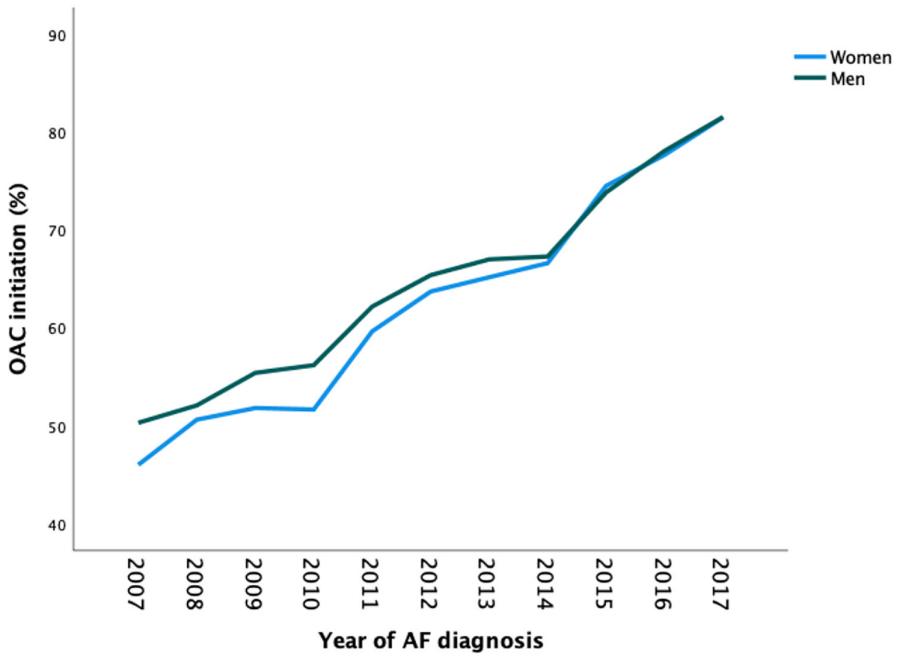

FIGURE 2 Trends in the initiation of OAC therapy within 1-year follow-up from AF diagnosis among patients eligible for OAC therapy according to the contemporary guidelines.

when compared to men (Table 2 and Figure S4). However, after adjusting for age and stroke risk factors (Model 1), this association resolved completely, and after further adjusting for confounding factors (Model 2), female sex was associated with a slightly lower rate of OAC initiation. These adjusted associations were similar in the subset of patients eligible for OAC therapy, but in this patient group female sex was associated with a lower OAC initiation rate also before adjustments (Table 2).

A significant interaction between AF diagnosis year and sex was observed ($p < 0.001$). In the overall cohort, the annual unadjusted hazard of OAC initiation was higher

TABLE 2 Initiation of OAC therapy in men and women during the overall study period.

	Events	Patient years (1000 years)	Incidence (per patient year)	Unadjusted HR	Adjusted HR (Model 1)	Adjusted HR (Model 2)
Overall cohort						
Men	79,743	177	0.45 (0.45–0.45)	(Reference)	(Reference)	(Reference)
Women	82,112	144	0.57 (0.56–0.57)	1.08 (1.07–1.10)	1.00 (0.99–1.01)	0.97 (0.96–0.98)
Patients eligible for OAC therapy						
Men	55,895	62	0.90 (0.89–0.91)	(Reference)	(Reference)	(Reference)
Women	72,040	93	0.78 (0.77–0.78)	0.94 (0.93–0.95)	1.00 (0.99–1.01)	0.97 (0.96–0.98)

Abbreviation: HR, hazard ratio.

Note: 95% confidence intervals in parenthesis. HRs estimated by cause-specific hazards with all-cause death as competing event. Model 1 adjusted for calendar year of AF diagnosis, age, hypertension, diabetes, heart failure, prior ischemic stroke or transient ischemic attack and vascular disease and Model 2 additionally for prior bleeding, alcohol use disorder, renal failure, liver cirrhosis or failure, cancer, dementia, psychiatric disorders and income level (divided into tertiles).

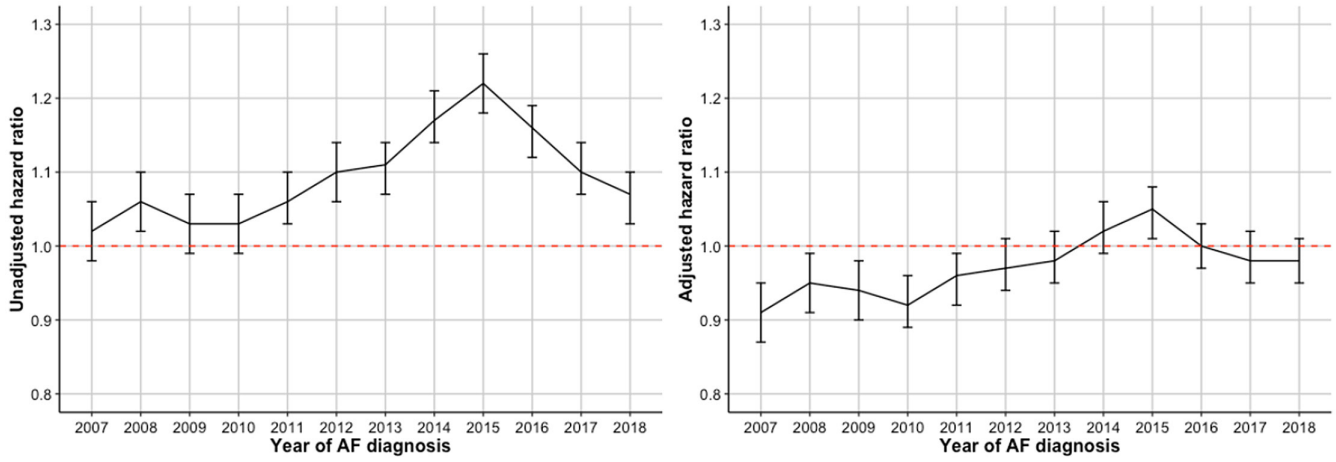

FIGURE 3 Unadjusted (left panel) and adjusted (right panel) hazard ratios with 95% confidence intervals of OAC initiation comparing women to men (red line as reference) according to the year of AF diagnosis in the overall cohort.

in women compared to men throughout the observation period, peaking in 2015. However, the adjusted HRs for women were lower until 2012, showing a marginal increase above that of men in 2015 and subsequently returning to a level comparable to men in the end of the study period (Figure 3). In the subset of patients eligible for OAC therapy according to the contemporary ESC guidelines, the unadjusted hazard of OAC initiation was lower in women compared to men until 2014 and thereafter comparable with men. After adjusting for confounding factors, female sex was associated with a lower OAC initiation rate only from 2010 to 2013, while displaying otherwise a comparable hazard to men (Figure 4).

4 | DISCUSSION

This nationwide retrospective cohort study investigated sex-related disparities in the initiation of OAC therapy among patients diagnosed with AF in Finland between 2007 and 2018. While women were overall slightly more likely to receive OAC therapy, this seemed to be driven by their higher age and stroke risk. In the adjusted analyses covering the whole study period, female sex was associated with a marginally lower initiation of OAC therapy. However, the gender disparities appeared to be more pronounced in the first half of the study period, eventually reaching parity during the observation period. Additionally, we observed that the broad adoption of DOACs for stroke prevention was slightly slower in women than in men.

To the best of our knowledge, this is the first study to investigate sex-specific temporal trends in the utilization of OAC therapy within a nationwide study sample encompassing all patients with AF from all levels of care.[26] Prior research in this area may have been susceptible to selection and information biases stemming from limited patient populations and reliance on only hospital-level data.[4,29–31] Indeed, patients treated solely in primary care are typically older high-risk individuals, and the lack of

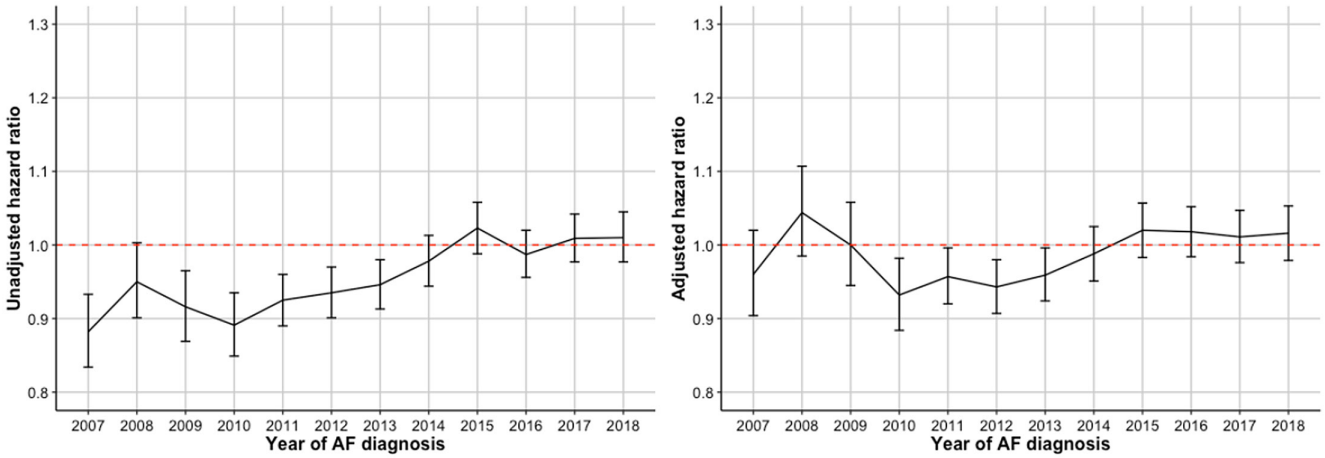

FIGURE 4 Unadjusted (left panel) and adjusted (right panel) hazard ratios with 95% confidence intervals of OAC initiation comparing women to men (red line as reference) according to the year of AF diagnosis including only patients recommended to receive OAC therapy according to the contemporary guidelines.

primary-care data may significantly compromise the general interpretation of previous findings. Thus, the present study's findings substantially enhance our understanding of the real-life implementation of clinical practice guidelines regarding OAC utilization in men and women with AF on a nationwide level.

Reflecting the progressively revised recommendations for stroke prevention in the clinical practice guidelines, the proportion of patients eligible for OAC therapy increased considerably during the study period, especially among women and this was accompanied by a substantial increase in OAC therapy initiation in both men and women.[17,18] During the early stages of the study period, despite the more stringent indications for anticoagulation, underutilization of OAC therapy was prevalent, particularly in women. This finding is consistent with previous reports from other countries indicating lower OAC utilization in women compared to men.[29–32] Notably, we observed that by the end of the observation period, there was no longer an association between female sex and lower utilization of OACs, indicating the resolution of sex-related disparities in stroke prevention during our study period. This trend may at least in parts reflect the implementation of the CHA_2DS_2-VASc score, which includes female sex as one of the risk factors.[17] Furthermore, the increasing awareness of gender disparities in health more broadly may have also played a role in the observed decline in the disparities in the use of OAC therapy.[24] A similar resolution of sex-related disparities in the utilization of OAC therapy, as observed in our study, has not been reported elsewhere. Furthermore, although we observed that the adoption of DOACs into the mainstream of OAC therapy was slightly slower among women, meaningful gender disparities in the overall use of OAC therapy were no longer seen in the DOAC era.

The adjusted sex-related disparities in OAC use at the beginning of the study period were more evident when all patients with incident AF were included in the analyses, as compared to the analyses covering only the patients eligible for anticoagulation according to the contemporary guidelines (Figures 3 and 4). Thus, although it seems retrospectively that stroke prevention was inferior in women compared to men during the early stages of the study period, there actually appears to have been only small gender inequality in the implementation of the clinical practice guidelines of the time. Indeed, in the subset of OAC eligible patients, signals of gender inequality were observed only from 2010 to 2013, possibly reflecting the rise in the proportion of women recommended to receive OACs and a slow implementation of the 2010 guidelines. Additionally, the initially lower OAC use in women eligible for OAC therapy appears to be largely explained by factors other than sex, as gender disparities was not observed during the first years of the study period in the adjusted analyses.

A particular strength of the current study is the coverage of all patients diagnosed with AF from all levels of care in Finland, enabling a uniquely comprehensive view of real-life treatment patterns on a nationwide level. Nevertheless, the limitations of our study need to be acknowledged, the most important of which are the challenges inherent in register-based retrospective cohort studies. Thus, information bias may be present in the used administrative data due to inaccurate recording. Furthermore, while the data we used included comprehensive information on claimed prescriptions, encompassing all OAC purchases nationwide, we did not have information on whether the patients actually took the purchased medications. We also lacked information on the specific subtypes of AF, including atrial flutter,

but the subtype does not meaningfully affect the need of OAC therapy. Additionally, we lacked data on the actual patient-level reasons for withholding OAC therapy. Moreover, the adjusted analyses did not incorporate variables related to pregnancy status or gynaecological bleedings. Finally, although the linked registry data allowed us to adjust the regressions for a vast number of potentially influencing factors, the possibility of residual confounding by other unmeasured factors cannot be excluded.

In conclusion, this nationwide cohort study encompassing all patients with incident AF in Finland from 2007 to 2018 found that although female sex was initially associated with a slightly lower initiation of OAC therapy, the sex-related disparities resolved over the course of the study period. Furthermore, when considering the progressive updates in the recommendations for OAC therapy in patients with AF throughout the study period, there seems to have been only small gender inequality in the real-life implementation of the clinical practice guidelines.

FUNDING INFORMATION

This work was supported by the Aarne Koskelo Foundation, The Finnish Foundation for Cardiovascular Research, and Helsinki and Uusimaa Hospital District research fund (TYH2019309).

CONFLICT OF INTEREST STATEMENT

Konsta Teppo: Research Grants: The Finnish Foundation for Cardiovascular Research, Aarne and Aili Turunen Foundation. Jussi Jaakkola: none. Olli Halminen: none. Janne Kinnunen: none. Jukka Putaala: Speaker: Bayer, Boehringer-Ingelheim, BMS-Pfizer, Abbott; Advisory board: Portola, Novo Nordisk, Herantis Pharma; Visiting editor: Terve Media; Stock ownership: Vital Signum. Pirjo Mustonen: Consultant: Roche, BMS-Pfizer-alliance, Novartis Finland, Boehringer Ingelheim, MSD Finland. Jari Haukka: Consultant: Research Janssen R&D; Speaker: Bayer Finland. Birgitta Salmela: Speaker (BMS, Boehringer Ingelheim, Pfizer); Advisory board (Pfizer) Miika Linna: Speaker: BMS-Pfizer-alliance, Bayer, Boehringer-Ingelheim. Juha Hartikainen: Research grants: The Finnish Foundation for Cardiovascular Research, EU Horizon 2020, EU FP7. Advisory Board Member: BMS-Pfizer-alliance, Novo Nordisk, Amgen. Speaker: Cardiome, Bayer. K.E. Juhani Airaksinen: Research grants: The Finnish Foundation for Cardiovascular Research; Speaker: Bayer, Pfizer and Boehringer-Ingelheim. Member in the advisory boards: Bayer, Pfizer and AstraZeneca. Mika Lehto: Consultant: BMS-Pfizer-alliance, Bayer, Boehringer-Ingelheim, and MSD; Speaker: BMS-Pfizer- alliance, Bayer, Boehringer Ingelheim, MSD, Terve Media and Orion Pharma. Research grants: Aarne Koskelo Foundation, The Finnish Foundation for Cardiovascular Research, and Helsinki and Uusimaa Hospital District research fund, Boehringer-Ingelheim.

DATA AVAILABILITY STATEMENT

Because of the sensitive nature of the data collected for this study, requests to access the dataset from qualified researchers trained in human subject confidentiality protocols may be sent to the Finnish national register holders (KELA, Finnish Institute for Health and Welfare, Population Register Center and Tax Register) through Findata (https://findata.fi/en/).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Teppo K, Airaksinen KEJ, Jaakkola J, et al. Temporal trends of gender disparities in oral anticoagulant use in patients with atrial fibrillation. *Eur J Clin Invest*. 2024;54:e14107. doi:10.1111/eci.14107