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

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

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

Published under the following license:
CC BY

Please cite the original version:

This material is protected by copyright and other intellectual property rights, and duplication or sale of all or part of any of the repository collections is not permitted, except that material may be duplicated by you for your research use or educational purposes in electronic or print form. You must obtain permission for any other use. Electronic or print copies may not be offered, whether for sale or otherwise to anyone who is not an authorised user.
Temporal trends of gender disparities in oral anticoagulant use in patients with atrial fibrillation


1Heart Centre, Turku University Hospital and University of Turku, Turku, Finland
2Turku University Hospital and University of Turku, Turku, Finland
3Aalto University, Espoo, Finland
4Heart Center, Department of Internal Medicine, Päijät-Häme Central Hospital, Lahti, Finland
5University of Helsinki, Helsinki, Finland
6Department of Neurology, Helsinki University Hospital and University of Helsinki, Helsinki, Finland
7University of Eastern Finland, Kuopio, Finland
8Heart and Lung Center, Helsinki University Hospital and University of Helsinki, Helsinki, Finland
9Kuopio University Hospital and University of Eastern Finland, Kuopio, Finland
10Jorvi Hospital, Department of Internal Medicine, HUS Helsinki University Hospital and University of Helsinki, Helsinki, Finland

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...
1 | INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia, affecting up to 5.2% of the adult population. It represents a major cause of ischemic stroke and is in addition associated with dementia, hospitalizations and higher mortality. 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.

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. Therefore, in 2010, female sex was incorporated into the CHA2DS2-VASc stroke risk score, which was subsequently adopted to the guidelines on AF management and became widely used in clinical practice. 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.

Sex-related disparities have been reported in the management and prognosis of several medical conditions. Likewise, there are reports of lower use of OAC therapy among women compared to men in patients with AF. 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. 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. 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.

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. 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
score ≥2 until 1 September 2010, followed by CHA₂DS₂-VASc score ≥2 until 1 September 2016, and thereafter, CHA₂DS₂-VASc score ≥2 for men and CHA₂DS₂-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 CHA₂DS₂-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).
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).

### TABLE 1 Baseline characteristics of the study cohort.

<table>
<thead>
<tr>
<th></th>
<th>Women</th>
<th>Men</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>114,823</td>
<td>114,747</td>
<td></td>
</tr>
<tr>
<td>Mean age, years</td>
<td>76.6 (11.8)</td>
<td>68.9 (13.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Income quartiles</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>First (lowest)</td>
<td>46.0</td>
<td>22.1</td>
<td></td>
</tr>
<tr>
<td>Second</td>
<td>33.2</td>
<td>31.8</td>
<td></td>
</tr>
<tr>
<td>Third (highest)</td>
<td>20.7</td>
<td>46.1</td>
<td></td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any vascular disease</td>
<td>27.0</td>
<td>29.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>20.7</td>
<td>22.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>49.1</td>
<td>46.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart failure</td>
<td>19.3</td>
<td>15.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>80.4</td>
<td>67.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prior IS or TIA</td>
<td>16.8</td>
<td>14.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Abnormal liver function</td>
<td>0.4</td>
<td>0.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Abnormal renal function</td>
<td>3.6</td>
<td>4.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Alcohol use disorder</td>
<td>1.6</td>
<td>6.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cancer</td>
<td>22.1</td>
<td>19.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dementia</td>
<td>6.7</td>
<td>3.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prior bleeding</td>
<td>9.1</td>
<td>12.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Psychiatric disorder</td>
<td>13.4</td>
<td>13.6</td>
<td>0.05</td>
</tr>
<tr>
<td>Risk scores</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean modified HAS-BLED score</td>
<td>2.6 (0.9)</td>
<td>2.4 (1.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean CHA2DS2-VASc score</td>
<td>4.2 (1.6)</td>
<td>2.6 (1.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stroke risk categories</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Low stroke risk</td>
<td>4.3</td>
<td>12.4</td>
<td></td>
</tr>
<tr>
<td>Moderate stroke risk</td>
<td>10.7</td>
<td>17.7</td>
<td></td>
</tr>
<tr>
<td>High stroke risk</td>
<td>85.0</td>
<td>70.0</td>
<td></td>
</tr>
</tbody>
</table>

Note: Values denote proportions (%) or mean (standard deviation). Abbreviations: CHA2DS2-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 CHA2DS2-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.
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...
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. 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. Indeed, patients treated solely in primary care are typically older high-risk individuals, and the lack of
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. 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. 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 CHA2DS2-VASC score, which includes female sex as one of the risk factors. 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**


**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/).

**ORCID**

Konsta Teppo https://orcid.org/0000-0002-4460-0994
K. E. Juhani Airaksinen https://orcid.org/0000-0002-0193-568X
Olli Halminen https://orcid.org/0000-0001-9266-8435
Elis Kouki https://orcid.org/0000-0002-5759-0916
Jari Haukka https://orcid.org/0000-0003-1450-6208
Jukka Putaatla https://orcid.org/0000-0002-6630-6104
Miika Linna https://orcid.org/0000-0002-7660-2484
Aapo L. Aro https://orcid.org/0000-0001-7030-6740
Pirjo Mustonen https://orcid.org/0000-0003-1319-0248
Juha Hartikainen https://orcid.org/0000-0003-0847-107X
Mika Lehto https://orcid.org/0000-0002-8691-5142

**REFERENCES**


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