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Socioeconomic factors and bleeding events in patients with incident atrial fibrillation: A Finnish nationwide cohort study

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ABSTRACT

Background: Low socioeconomic status has been associated with higher risk of ischemic stroke and death in patients with atrial fibrillation (AF). However, whether socioeconomic status affects risk of bleeding events is unknown. We assessed the hypothesis that low income and educational attainment are associated with higher risk of bleeding in patients with AF.

Methods: The registry-based FinACAF study covers all patients with AF in Finland during 2007–2018. Patients were divided into income quartiles and three categories based on their educational attainment. Outcomes of interest were the first-ever gastrointestinal (GI), intracranial (IC) and any bleeding.

Results: We identified 205 019 patients (50.9 % female; mean age 72.3 (SD 13.4) years) with incident AF without prior bleeding. Mean follow-up time was 4.0 (SD 3.2) years, during which 25 013 (12.2 %) patients experienced first-ever any bleeding (incidence rate 3.07 (95 % CI 3.03–3.10) /100 patient-years). Low income was independently associated with hazard of any bleeding as well as GI and IC bleeding (adjusted hazard ratios (HRs) comparing lowest vs highest income quartile: 1.13 (1.08–1.17), 1.32 (1.23–1.41) and 1.15 (1.06–1.24), respectively). Income-related bleeding disparities were larger among younger patients under 65 years and among men. Education-related bleeding disparities were smaller than income related-disparities (adjusted HRs comparing lowest vs highest educational category: any bleeding 1.06 (1.02–1.11), GI bleeding 1.16 (1.08–1.24), IC bleeding 1.10 (0.93–1.09))

Conclusions: Patients with AF and low income are at higher risk of bleeding, especially GI bleeding.

1. Introduction

Atrial fibrillation (AF), the most common sustained cardiac arrhythmia with a prevalence as high as 4.1 %, is associated with increased risk of ischemic stroke and mortality [1,2]. Fortunately, oral anticoagulant (OAC) therapy effectively reduces both the risk of stroke and death in patients with AF and high stroke risk, but it also predisposes patients to bleeding events [1,3]. Therefore, assessment of patient's

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bleeding risk is essential for optimal stroke prevention therapy, and validated risk stratification tools have been developed to guide clinical decision making [4].

Socioeconomic inequalities in health are widespread, also affecting patients with AF. Socioeconomic disparities have been reported in the treatment of AF, as well as in stroke and mortality outcomes [5–9]. However, there is a paucity of information on the association of socioeconomic status and bleeding risk. The present nationwide cohort study covering all patients with incident AF in Finland aimed to assess whether patients' income and educational levels affect bleeding risks in these patients.

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 including all patients with an AF diagnosis in Finland during 2004–2018 [2]. Patients were identified from all available national health care registers (hospitalizations and outpatient specialist visits: HILMO; primary health care: AvoHILMO; and National Reimbursement Register upheld by Social Insurance Institute: KELA). The inclusion criterion for the cohort was an International Classification of Diseases, Tenth Revision (ICD-10) diagnosis code I48 (including atrial fibrillation and atrial flutter, together referred as AF) recorded between 2004 and 2018 and cohort entry occurred on the date of the first recorded AF diagnosis. The exclusion criteria were permanent migration abroad before December 31st 2018 and age 20<1 years at AF diagnosis. Follow-up continued until death or 31st December 2018, whichever occurred first. The current substudy was conducted within a cohort of patients with incident AF between 2007 and 2018, established in previous studies on the FinACAF cohort [9–12]. Patients with prior bleeding events before the beginning of follow-up were excluded. Sensitivity analyses were performed among patients < 65 years and ≥ 65 years at AF diagnosis as well as among men and women. The patient selection process is summarized in Supplementary Fig. S1.

2.2. Income and educational levels

The patients' individual highest annual taxable income (in 1000-euro accuracy) during 2004–2018 was derived from the national Tax Register. The annual income was capped to a maximum of 100 000 euros to avoid patients' identifiability due to high incomes. To account for changes in income over time and age, patients were divided into age group and AF diagnosis year specific income quartiles, i.e., each 10-year age group during each cohort entry year was divided into income quartiles using age group and entry year specific cut-points [13]. The cohorts in the sensitivity analyses were divided separately into income quartiles in a similar manner.

The patients' highest achieved educational level categorized according to the International Standard Classification of Education (ISCED) was obtained from Statistics Finland [14]. Educational level was divided into three categories: Category 1: ISCED 0–2 (no registered, preprimary, primary, or lower secondary education); Category 2: ISCED 3 (Upper secondary or vocational education); Category 3: ISCED 5–8 (tertiary, Bachelor's-level, Master's-level, or doctoral level education). ISCED category 4 does not exist in Finland.

2.3. Outcomes

The outcomes of interest were first-ever bleeding from any anatomical site, gastrointestinal (GI) bleeding and intracranial (IC) bleeding events. The outcome was considered to occur on the date of first recorded bleeding diagnosis. The diagnosis codes and dates were searched from the aforementioned hospital care register. The used ICD-10 codes are summarized in Supplementary Table S1.

2.4. Study Ethics

The study protocol was approved by the Ethics Committee of the Medical Faculty of Helsinki University, Helsinki, Finland (nr. 15/2017) and granted 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). The patients' 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.

2.5. Statistical analysis

The chi-square test was used to compare differences between proportions, and the one-way analysis of variance to analyze continuous variables. Cox proportional hazards model was used to estimate the unadjusted and adjusted hazard ratios (HR) for bleeding events. In addition to income and educational levels, the adjusted analyses with the Cox regression model included the following patient characteristics at cohort entry: age, gender, calendar year of AF diagnosis, dementia, cancer, alcohol use disorder, prior stroke, abnormal liver function, abnormal kidney function, diabetes, hypertension, any vascular disease, heart failure and use of OAC. OAC exposure was treated as a time-dependent variable, and was considered to start from the first OAC purchase date (warfarin, dabigatran, apixaban, rivaroxaban or edoxaban) and continue until 135 days after the last OAC purchase. The 135-day interval was chosen since in Finland it is possible to purchase drugs with reimbursement for a maximum of 90 days and an additional 45-day grace period was allowed to cover possible stockpiling and differences in warfarin dosing. An interaction term between income/educational categories and follow-up time, along with the inspection of log-negative log survival curves, indicated that the proportional hazards assumption was met. The definitions of the comorbidities are displayed in Supplementary Table S1. Statistical analyses were performed with the SPSS Statistics software (version 27.0, SPSS, Inc., Armonk, NY) and R (version 4.0.5, https://www.R-project.org).

3. Results

We identified 205 019 patients (50.9 % female; mean age 72.3 (SD 13.4) years) with incident AF during 2007–2018, with a mean follow-up time of 4.0 (SD 3.2) years in the any bleeding analyses. Patients with higher income were more often male, had higher education, and lower prevalence of cardiovascular comorbidities than patients with lower income. Similarly, patients with higher education were more often male and had higher income and lower prevalence of comorbidities. Additionally, patients in the highest educational category were substantially younger than patients with lower educational background (Table 1). Overall, 25 013 (12.2 %; incidence rate (95 % CI) 3.07 (3.03–3.10) /100 patient-years) patients experienced their first-ever any bleeding event during follow-up, and GI and IC bleeding events were observed in 8 580 (4.2 %) and 6 109 (3.0 %) patients, respectively. OAC therapy was initiated in 147 098 patients (71.1 %), and the initial anticoagulant was warfarin in 68.2 % and direct oral anticoagulant in 31.8 % of patients.

The crude incidence of all bleeding categories were generally higher in patients with lower income and educational levels, although the trend was non-linear in the crude incidence of IC bleeding (Fig. 1, Tables 2 and 3). The crude proportion of patients experiencing any bleeding within one year follow-up increased across the observation period, and notable inconsistency in the annual income-related disparities was observed,

Table 1
Descriptive characteristics of the study cohort according to income and educational levels.

	Income quartiles					Educational categories			
	1st (lowest)	2nd	3rd	4th (highest)	P-value	1st (lowest)	2nd	3rd (highest)	P-value
	n = 53 376	n = 49 311	n = 51 308	n = 51 024		n = 106 090	n = 55 948	n = 42 981	
Mean annual income (thousands of euros)	3.1 (5.4)	12.0 (9.7)	21.7 (12.8)	51.5 (26.5)	< 0.001	12.5 (16.9)	22.9 (21.1)	43.9 (27.7)	< 0.001
Demographics									
Mean age, years	73.4 (13.4)	72.0 (13.4)	71.9 (13.3)	71.9 (13.3)	< 0.001	77.2 (10.8)	67.0 (13.8)	67.0 (13.8)	< 0.001
Female sex	33 896 (63.5)	28 054 (56.9)	24 691 (48.1)	17 737 (34.8)	< 0.001	61 058 (57.6)	25 750 (46.0)	17 570 (40.9)	< 0.001
Educational categories					< 0.001				
1st	36 004 (67.5)	28 699 (58.2)	25 864 (50.4)	15 523 (30.4)		N/A	N/A	N/A	
2nd	14 494 (27.2)	15 471 (31.4)	15 087 (29.4)	10 896 (21.4)		N/A	N/A	N/A	
3rd	2 878 (5.4)	5 141 (10.4)	10 357 (20.2)	24 605 (48.2)		N/A	N/A	N/A	
Income quartiles									< 0.001
1st	N/A	N/A	N/A	N/A		36 004 (33.9)	14 494 (25.9)	2 878 (6.7)	
2nd	N/A	N/A	N/A	N/A		28 699 (27.1)	15 471 (27.7)	5 141 (12.0)	
3rd	N/A	N/A	N/A	N/A		25 864 (24.4)	15 087 (27.0)	10 357 (24.1)	
4th	N/A	N/A	N/A	N/A		15 523 (14.6)	10 896 (19.5)	24 605 (57.2)	
Comorbidities									
Abnormal liver function	281 (0.5)	172 (0.3)	154 (0.3)	134 (0.3)	< 0.001	340 (0.3)	246 (0.4)	155 (0.4)	< 0.001
Abnormal renal function	2 208 (4.1)	1 719 (3.5)	1 657 (3.2)	1 503 (2.9)	< 0.001	4 386 (4.1)	1 659 (3.0)	1 042 (2.4)	< 0.001
Alcohol use disorder	3 291 (6.2)	1 597 (3.2)	1 278 (2.5)	982 (1.9)	< 0.001	3 230 (3.0)	2 729 (4.9)	1 189 (2.8)	< 0.001
Any vascular disease	15 809 (29.6)	13 383 (27.1)	13 374 (26.1)	12 176 (23.9)	< 0.001	34 079 (32.1)	12 718 (22.7)	7 945 (18.5)	< 0.001
Cancer	9 947 (18.6)	9 271 (18.8)	10 018 (19.5)	10 818 (21.2)	< 0.001	23 019 (21.8)	8 923 (15.9)	8 112 (18.9)	
Dementia	3 271 (6.1)	2 370 (4.8)	2 242 (4.4)	1 974 (3.9)	< 0.001	7 195 (6.8)	1 591 (2.8)	1 071 (2.5)	< 0.001
Diabetes	13 093 (24.5)	10 767 (21.8)	10 176 (19.8)	8 845 (17.3)	< 0.001	25 008 (23.6)	11 121 (19.9)	6 672 (15.5)	< 0.001
Dyslipidemia	24 591 (46.1)	23 492 (47.6)	24 398 (47.6)	23 767 (46.6)	< 0.001	53 292 (50.2)	24 978 (44.6)	17 978 (41.8)	< 0.001
Heart failure	11 684 (21.9)	8 399 (17.0)	7 515 (14.6)	6 368 (12.5)	< 0.001	22 638 (21.3)	7 348 (13.1)	3 980 (9.3)	< 0.001
Hypertension	40 018 (75.0)	36 672 (74.4)	37 461 (73.0)	36 003 (70.6)	< 0.001	82 263 (77.5)	39 056 (69.8)	28 835 (67.1)	< 0.001
Prior ischemic stroke	5 692 (10.7)	4 836 (9.8)	4 786 (9.3)	4 390 (8.6)	< 0.001	11 949 (11.3)	4 672 (8.4)	3 083 (7.2)	< 0.001
Prior myocardial infarction	5 150 (9.6)	4 107 (8.3)	4 041 (7.9)	3 571 (7.0)	< 0.001	10 622 (10.0)	3 944 (7.0)	2 303 (5.4)	< 0.001
Risk scores									
CHA_2DS_2-VASc score	3.7 (1.9)	3.4 (1.8)	3.3 (1.9)	3.0 (1.8)	< 0.001	3.9 (1.7)	2.8 (1.9)	2.6 (1.7)	< 0.001
Modified HAS-BLED score	2.4 (1.0)	2.4 (1.0)	2.3 (1.0)	2.3 (1.0)	< 0.001	2.5 (0.9)	2.2 (1.0)	2.1 (1.0)	< 0.001
Medications									
Antiplatelet/NSAIDs at baseline	16 087 (30.1)	15 448 (31.3)	16 089 (31.4)	15 296 (30.0)	< 0.001	32 078 (30.2)	18 202 (32.5)	12 640 (29.4)	< 0.001
OAC initiation during follow-up	36 336 (68.1)	35 623 (72.2)	37 746 (73.6)	37 393 (73.3)	< 0.001	77 285 (72.8)	39 804 (71.1)	30 009 (69.8)	< 0.001

Values denote n (%) or mean (standard deviation). Abbreviations: CHA_2DS_2-VASc, congestive heart failure, hypertension, age ≥ 75 years, diabetes, history of stroke or TIA, vascular disease, age 65–74 years, sex category (female); modified HAS-BLED score, hypertension, abnormal renal or liver function, prior stroke, bleeding history, age > 65 years, alcohol abuse, concomitant antiplatelet/NSAIDs (no labile INR, max score 8); NSAID, nonsteroidal anti-inflammatory drug; OAC, oral anticoagulant.

while the education-related disparities remained more consistent (Fig. 2). Additionally, in the sensitivity analysis, the disparities in the crude incidence of any bleeding were more evident in patients under 65 years than in older patients (Supplementary Table S2 and Supplementary Fig. S2).

In the adjusted analyses, both lower income and educational levels were associated with a consistently higher hazard of any and GI bleedings, whereas a similar dose–response association was not observed with IC bleeding, where only the lowest income quartile was associated with a higher hazard of IC bleeding, when compared to the highest income quartile (Table 3). Exposure to OACs was associated with the hazard of any bleeding (adjusted HR (95 % CI) 1.20 (1.17–1.23)). In the sensitivity analyses, after adjusting for confounding factors, the income-related disparities were larger among younger patients under 65 years as well as among men when compared to women (Supplementary Tables S2 and S3).

4. Discussion

This nationwide cohort study demonstrated socioeconomic disparities in the incidence of first-ever bleeding events in patients with incident AF. Overall, patients with low income and educational attainment experienced more bleeding events than patients with higher income and education. After adjusting for confounding factors, the most prominent association was observed between low income and risk of GI bleeding, whereas education-related disparities were somewhat smaller. Income-

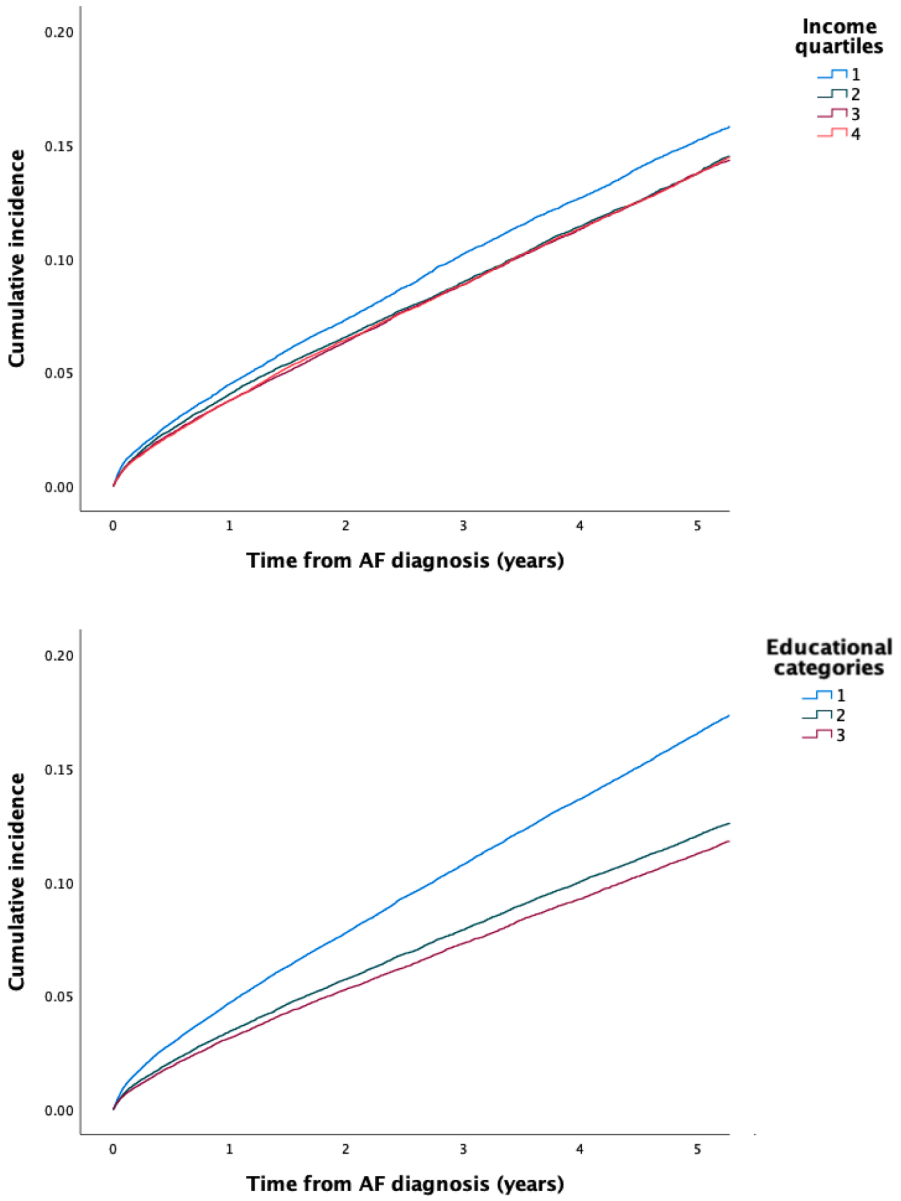

Fig. 1. Crude cumulative incidence curves of any bleeding according to income (above panel) and educational levels (below panel).

related disparities in any bleeding incidence were most profound among working-aged patients under 65 years.

Previous research on the association of socioeconomic factors and outcomes in patients with AF has focused on ischemic stroke and mortality, while information on bleeding outcomes is limited [9,15]. A small (n = 7 274) cohort study conducted in the United States reported higher rate of any bleeding among anticoagulated patients with AF residing in deprived areas [16]. Additionally, in a Canadian study on elderly patients with AF, low neighborhood-level income was associated with higher risk of fatal bleeding [17]. However, these studies may have been prone to major selection, confounding, and information biases owing to selected patient populations, insufficient controlling for confounding factors, and use of only area-based socioeconomic data. Therefore, the current nationwide study with comprehensive individual-level data on all patients with AF considerably expands our understanding on the associations of income and education with bleeding events.

The largest income-related disparities were observed in GI bleedings; patients in the lowest income quartile had a 32 % higher adjusted hazard of GI bleeding when compared to the highest income quartile. The disparities in other bleeding categories were smaller, and when compared to the income-related disparities, the associations between educational attainment and bleeding risks were markedly smaller. Importantly, although the majority of bleeding events were observed among patients over 65 years, the income-related bleeding disparities were most evident among younger, working aged patients, as well as slightly larger among men than among women. These findings are in accordance with previous observations of larger socioeconomic health inequalities among working-aged individuals and men [9,18]. Of note, clear income-related bleeding disparities were observed even after controlling for an extensive set of patient characteristics, indicating that the bleeding risks associated with low income are not fully explained by the factors incorporated in the widely used bleeding risk stratification scores. The authors have previously reported high risk of ischemic stroke and death in patients with AF and low income within the FinACAF study cohort, in concordance with the high bleeding risks observed in the current study [9]. However, importantly, the adjusted stroke risk in the lowest income category was approximately 2-fold higher than in the highest income category, indicating that even though low income is also associated with bleeding, the risk of ischemic stroke predominates in the risk profile of these vulnerable patients.

Table 2
Crude incidence of bleeding according to income and educational levels.

	Any bleeding			GI bleeding			IC bleeding		
	Events, n (%)	P-years (100 years)	Incidence rate (per 100p-years)	Events, n (%)	P-years (100 years)	Incidence rate (per 100p-years)	Events, n (%)	P-years (100 years)	Incidence rate (per 100p-years)
Income quartiles									
4th	6 556 (12.8)	2188	3.00 (2.93–3.07)	1 958 (3.8)	2309	0.85 (0.81–0.89)	1 637 (3.2)	2323	0.71 (0.67–0.74)
3rd	6 304 (12.3)	2142	2.94 (2.87–3.02)	2 064 (4.0)	2251	0.92 (0.88–0.96)	1 474 (2.9)	2276	0.65 (0.62–0.68)
2nd	5 881 (11.9)	1955	3.01 (2.93–3.09)	2 064 (4.2)	2048	1.01 (0.97–1.05)*	1 395 (2.8)	2072	0.67 (0.64–0.71)
1st	6 272 (11.8)	1875	3.35 (3.26–3.43)*	2 494 (4.7)	1960	1.27 (1.22–1.32)*	1 603 (3.0)	1988	0.81 (0.77–0.85)*
Educational categories									
3rd	4 449 (10.4)	1873	2.38 (2.31–2.45)	1 311 (3.1)	1957	0.67 (0.64–0.71)	1 073 (2.5)	1968	0.55 (0.51–0.58)
2nd	6 076 (10.9)	2354	2.58 (2.52–2.65)*	2 033 (3.6)	2404	0.83 (0.79–0.86)*	1 382 (2.5)	2384	0.56 (0.53–0.89)
1st	14 488 (13.7)	3932	3.69 (3.63–3.75)*	5 236 (4.9)	4151	1.26 (1.23–1.30)*	3 654 (3.4)	4207	0.87 (0.84–0.90)*

Abbreviations: GI, gastrointestinal; IC, intracranial. 95 % confidence intervals in parenthesis. *=p < 0.001 when compared with the highest category. 1st indicates the lowest income and educational categories.

Table 3
Hazard ratios of bleeding according to income and educational levels.

	Any bleeding		GI bleeding		IC bleeding	
	Unadjusted HR	Adjusted HR	Unadjusted HR	Adjusted HR	Unadjusted HR	Adjusted HR
Income quartiles						
4th	(Reference)	(Reference)	(Reference)	(Reference)	(Reference)	(Reference)
3rd	0.98 (0.95–1.02)	1.01 (0.97–1.05)	1.08 (1.01–1.15)	1.05 (0.98–1.12)	0.92 (0.86–0.99)	0.95 (0.88–1.03)
2nd	1.00 (0.96–1.03)	1.07 (1.03–1.11)	1.18 (1.11–1.25)	1.16 (1.08–1.24)	0.95 (0.89–1.02)	1.03 (0.96–1.12)
1st	1.10 (1.06–1.14)	1.13 (1.08–1.17)	1.46 (1.38–1.55)	1.32 (1.23–1.41)	1.14 (1.06–1.22)	1.15 (1.06–1.24)
Educational categories						
3rd	(Reference)	(Reference)	(Reference)	(Reference)	(Reference)	(Reference)
2nd	1.09 (1.04–1.13)	1.05 (1.01–1.10)	1.23 (1.15–1.32)	1.10 (1.02–1.19)	1.02 (0.94–1.10)	1.00 (0.92–1.09)
1st	1.53 (1.48–1.59)	1.06 (1.02–1.11)	1.85 (1.74–1.97)	1.16 (1.08–1.24)	1.59 (1.48–1.70)	1.01 (0.93–1.09)

Abbreviations: GI, gastrointestinal; IC, intracranial; HR, hazard ratio. 95% confidence intervals in parenthesis. HRs estimated by Cox regression and adjusted analyses included the following variables: age, gender, cohort entry year, dementia, cancer, alcohol use disorder, prior stroke, abnormal liver function, abnormal kidney function, diabetes, hypertension, any vascular disease, heart failure, use of oral anticoagulant, income quartiles and educational categories. 1st indicates the lowest income and educational categories.

The observed socioeconomic disparities in bleeding risks are likely multifactorial. Education-related disparities attenuated substantially after adjusting for other patient characteristics, suggesting that the observed crude disparities between educational categories were largely explained by differences in age and in the prevalence of other bleeding risk factors. Furthermore, patients with lower socioeconomic status may also have more often undiagnosed comorbidities and bleeding risk factors, and their modifiable risk factors may be inferiorly managed [19]. Indeed, low socioeconomic status has been associated with diminished access to preventative care, specialty care, and prescription medications [20–22]. Additionally, unhealthy life-style habits, such as tobacco use, are more common in patients with low socioeconomic status [23,24]. Moreover, the previously observed poorer anticoagulation control with warfarin and lower adherence to DOACs and other therapies may increase bleeding risks among patients with lower income and educational attainment [7,16,25,26].

Our findings must be interpreted bearing in mind the limitations of this study, especially the challenges inherent to registry-based retrospective cohort studies. Hence, our results represent associations and not necessarily causation, and information and confounding biases due to unmeasured or inappropriately recorded data may affect our results. Additionally, due to the limitations of our data, we focused the analyses on the first-ever bleeding event, and were unable to account for repeat bleeding episodes. Except for diagnosed alcohol use disorders, we lacked data on life-style related factors. Furthermore, although the regressions were adjusted for both cohort entry year and age, the secular trends in improving educational attainment and educational opportunities can modify the association between education and bleeding events. Moreover, since nonsteroidal anti-inflammatory drugs and low-dose acetylsalicylic acid are frequently purchased over the counter without prescription in Finland, we did not consider their use in the adjustments. Likewise, use of OACs is based on pharmacy claims, and the proportion of drugs truly taken is unknown. On the other hand, major strengths of our study are the large nationwide study sample, comprehensive data on medical records from all levels of care and individual-level socioeconomic data. Furthermore, the used national registries have been well-validated and have high diagnostic accuracy, especially regarding cardiovascular diseases [27].

The results of this nationwide retrospective cohort study among patients with incident AF without prior bleeding events accentuate higher bleeding risk, especially GI bleeding risk, in patients with low income. Additionally, low educational attainment was associated with slightly higher risk of GI and any bleeding. These findings highlight the importance of appropriate bleeding risk assessment and management of modifiable bleeding risk factors in patients with AF and low income. Policymakers should focus on reducing socioeconomic health disparities in patients with AF.

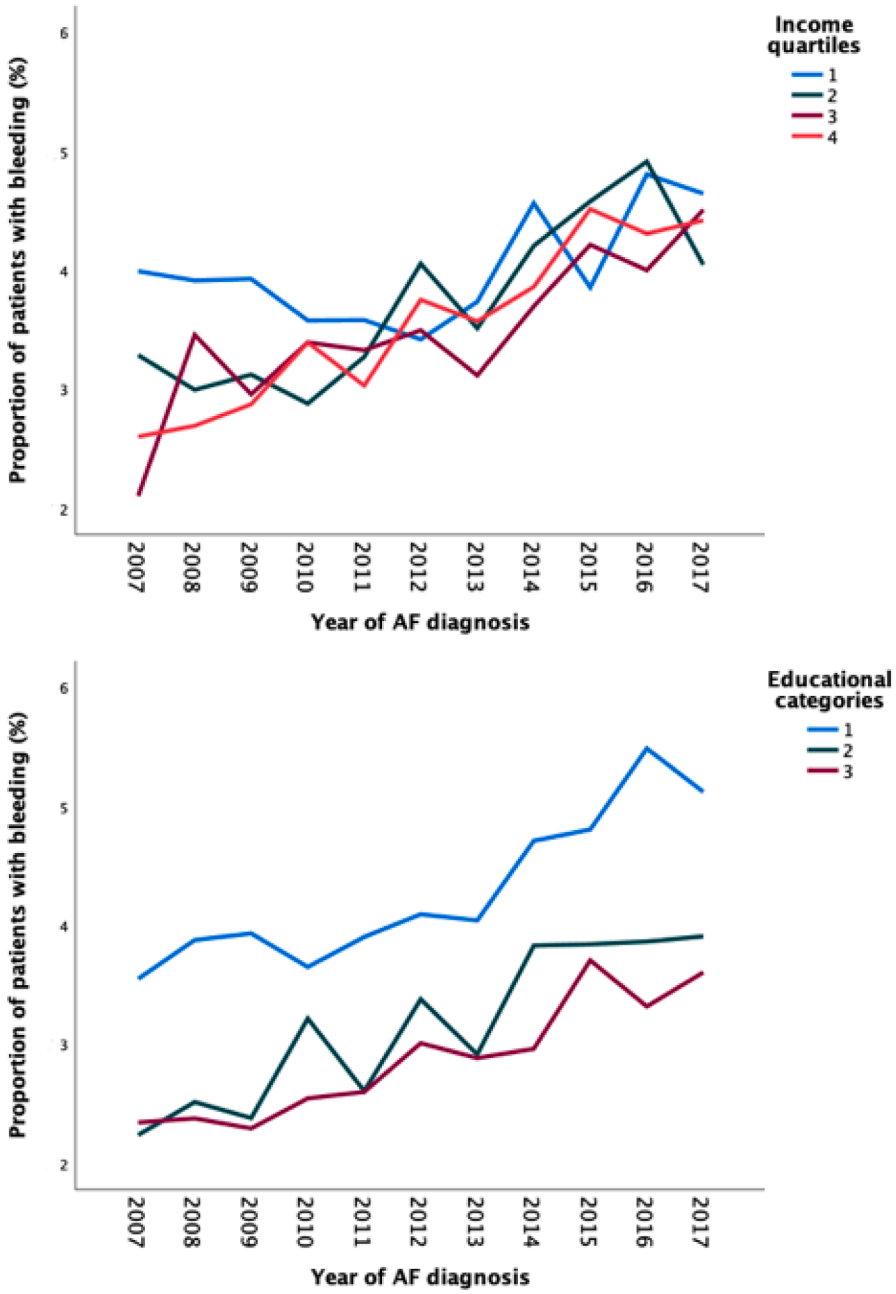

Fig. 2. Temporal trends in the proportion of patients with any bleeding within one year follow-up according to income (above panel) and educational levels (below panel).

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability Statement.

Because of the sensitive nature of the data collected for this study and the contracts with the Finnish registries, the data cannot be shared outside of the study group.

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Appendix A. Supplementary material

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