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ORIGINAL ARTICLE

Association of income and educational levels with adherence to direct oral anticoagulant therapy in patients with incident atrial fibrillation: A Finnish nationwide cohort study

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Abstract

Low socioeconomic status has been associated with poor outcomes in patients with atrial fibrillation (AF). However, little is known about socioeconomic disparities in adherence to stroke prevention with direct oral anticoagulants (DOACs). We assessed the hypothesis that AF patients with higher income or educational levels have better adherence to DOACs in terms of treatment implementation and persistence. The used nationwide registry-based FinACAF cohort covers all patients with incident AF starting DOACs in Finland during 2011–2018. The implementation analyses included 74 222 (mean age 72.7 ± 10.5 years, 50.8% female) patients, and persistence analyses included 67 503 (mean age 75.3 ± 8.9 years, 53.6% female) patients with indication for permanent anticoagulation (CHA_2DS_2-VASc score >1 in men and >2 in women). Patients were divided into income quartiles and into three categories based on their educational attainment. Therapy

Abbreviations: AF, atrial fibrillation; DOAC, direct oral anticoagulant; FinACAF, Finnish anticoagulation in atrial fibrillation; ICD-10, International Classification of Diseases, Tenth Revision; ISCED, International Standard Classification of Education; MPR, medication posession ratio; OAC, oral anticoagulant; VKA, vitamin-K anticoagulant.

implementation was measured using the medication possession ratio (MPR), and patients with MPR ≥0.90 were defined adherent. Persistence was measured as the incidence of therapy discontinuation, defined as the first 135-day period without DOAC purchases after drug initiation. Patients with higher income or education were consistently more likely adherent to DOACs in the implementation phase (comparing the highest income or educational category to the lowest: adjusted odds ratios 1.18 (1.12–1.25) and 1.21 (1.15–1.27), respectively). No association with income or educational levels was observed on the incidence of therapy discontinuation. In conclusion, we observed that income and educational levels both have independent positive association on the implementation of DOAC therapy but no association on therapy persistence in patients with AF.

KEYWORDS
adherence, atrial fibrillation, direct oral anticoagulants, educational level, income, persistence, socioeconomic status

1 | INTRODUCTION

Atrial fibrillation (AF), the most common cardiac arrhythmia, is associated with a five-fold increased risk of ischemic stroke as well as with stroke recurrence and mortality.[1,2] Fortunately, the adequate use of oral anticoagulant therapy (OAC) can effectively reduce the risk of ischemic stroke and death.[3] Current guidelines recommend the use of direct oral anticoagulants (DOACs) over vitamin-K anticoagulants (VKAs) as the first line anticoagulant due to their superior efficacy and safety profile.[4] Unlike VKAs, DOACs do not require regular dose monitoring, and the lack of these systematic check-ups has raised concerns about patients' sufficient adherence to DOAC therapy.

Adherence research guidelines recommend dividing medication adherence into three phases: initiation, implementation, and persistence, with implementation referring to how patient's actual dosing corresponds to the prescribed dosing between treatment initiation and discontinuation, and persistence to the length of time between initiation and discontinuation.[5] All aspects of adherence are crucial for effective stroke prevention with OACs in patients with AF since poor therapy implementation and persistence have been associated with higher mortality and ischemic stroke risk.[6-8]

Socioeconomic inequalities in health are a major challenge for public health, and their magnitude is affected by differences in health care financing mechanisms.[9-13] Finland has a public tax-funded health care with universal access, full coverage of public health insurance, and relatively high reimbursement rates of medical treatment.[14-16] Nevertheless, socioeconomic disparities are observed in Finland in terms of mortality, morbidity, and self-rated health.[17]

Previous literature has indicated poor outcomes in patients with AF and low socioeconomic status, and differences in the use of OAC therapy may be underlying these outcome disparities.[18,19] Indeed, previous studies have suggested that low income and educational levels are associated with lower rate of OAC therapy initiation in patients with AF. However, information on whether socioeconomic factors affect adherence to initiated OAC therapy is limited, especially regarding DOACs.[20] The present nationwide cohort study covering all AF patients in Finland aimed to assess the impact of patients' income and educational levels on the adherence to DOACs focusing on therapy implementation and persistence.

2 | MATERIALS AND METHODS

2.1 | Study population

The Finnish AntiCoagulation in Atrial Fibrillation (FinACAF) Study (ClinicalTrials Identifier: NCT04645537; ENCePP Identifier: EUPAS29845) is a retrospective nationwide cohort study covering all patients with diagnosed AF in Finland during 2004–2018.[21] 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 FinACAF cohort entry occurred at the date of the first recorded AF diagnosis. The exclusion criteria were permanent migration abroad before December 31st 2018 and age <18 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 of the FinACAF cohort.[22,23]

Patients not receiving DOACs during 2011–2018, when DOACs have been approved for stroke prevention in patients with AF, were excluded. Thereafter, we established two separate study cohorts for the analyses of implementation and persistence. In the implementation study cohort, we included only patients with more than one DOAC purchase since true implementation pattern of a long-term preventive therapy cannot be meaningfully determined from only one purchase. In the persistence study cohort, we included patients recommended to receive permanent OAC therapy according to the

contemporary guidelines of the study period, and therefore, females with CHA_2DS_2-VASc score ≤2 and males with CHA_2DS_2-VASc score ≤1 were excluded.[24,25] In this substudy, follow-up started on the date of the first DOAC purchase. The patient selection process is summarized in the Supplementary Figure 1.

2.2 | Income and educational levels

The patient's highest annual taxable income (in 1000-euro accuracy) during the FinACAF study's observation period 2004–2018 was obtained 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.[26] Divisions to income quartiles were performed separately in the implementation and persistence study cohorts.

The patients' highest achieved educational level categorized according to the International Standard Classification of Education (ISCED) was obtained from the Statistics Finland.[27] Educational level was divided into three categories: Category 1: ISCED 0–2 (preprimary, primary, and 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 | Adherence to DOACs

The present substudy focused on the implementation and persistence of initiated DOAC (apixaban, dabigatran, edoxaban, or rivaroxaban) therapy. The commonly used medication possession ratio (MPR) was used to quantify therapy implementation. The MPR of each patient was calculated by dividing the number of days covered with the sum of purchased daily doses during persistent therapy by the number of days between the first and the last DOAC purchase dates added with the days covered with the dose of the last purchase:

$$MPR = \frac{\textit{Days covered with the sum of daily doses}}{\textit{Days between first and last DOAC purchase plus the days covered with the daily dose from last DOAC purchase}}.$$

Medication possession ratio values were capped to a maximum of 1.0 and patients with MPR ≥0.90 were defined adherent, since MPR <0.90 has been associated with reduced efficacy of stroke prevention with DOACs.[6,28] We assessed treatment implementation during persistent DOAC use, i.e., between treatment initiation and discontinuation, and only DOAC purchases before therapy discontinuation were included in the MPR calculations. Discontinuation was defined as the first 135-day period without DOAC redemptions. The 135-day definition 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. Additionally, sensitivity analyses were performed including all DOAC purchases during entire follow-up instead of only drug purchases before the first discontinuation event.

In the persistence analyses, we determined the incidence of therapy discontinuation, i.e., non-persistence. The date of the first DOAC purchase was the index date and outcome was the first therapy discontinuation event. As stated above, discontinuation event was defined as the first 135-day period without DOAC redemptions and was considered to occur at the end of the 135-day period. Individuals switching to VKA during the 135-day period were censored, and those switching from one DOAC to another during the 135-day period were considered persistent. As a sensitivity analysis, we analyzed the rate of DOAC therapy cessation, considered to occur on the date of the last DOAC purchase in patients with at least six months of follow-up after the last purchase to ensure more definitive termination of stroke prevention. Additionally, patients initiating VKA after the last DOAC purchase were censored in the cessation analysis.

2.4 | Statistical analysis

Statistical analyses were performed with the IBM SPSS Statistics software (version 27.0, SPSS, Inc., Armonk, NY) and R (version 4.0.5, https://www.R-project.org). The chi-square test was used to compare differences between proportions, and the one-way analysis of variance to analyze continuous variables. MPR was non-normally distributed, and therefore, mean MPR between socioeconomic groups was compared using the Kruskal–Wallis test. Unadjusted and adjusted odds ratios (ORs) of adherence to DOAC therapy (MPR ≥0.90) for socioeconomic categories were calculated using the binary logistic regression. Poisson regression was used to estimate the crude incidence as well as the unadjusted and adjusted incidence rate ratios (IRRs) of therapy discontinuation for income and educational categories. The observation of discontinuation event may be hindered by mortality occurring during study period, and therefore, the Fine-Gray regression with all-cause death as competing event was used to estimate the unadjusted and adjusted subdistribution hazard ratios (SHRs) of DOAC therapy discontinuation for income and educational categories. In addition to income and educational levels, the analyses with the Fine-Gray and binary logistic regression models were adjusted for age (categorical variable in 10 year groups), sex, calendar year of DOAC initiation, stroke and bleeding risk factors (heart failure, hypertension, diabetes, prior stroke or transient ischemic attack, vascular disease, prior bleeding, alcohol abuse, renal failure and liver cirrhosis or failure, concomitant use of NSAIDs or antiplatelets), dementia, mental health conditions, dosage of the first

purchased DOAC (once or twice daily), previous use of VKAs and polypharmacy (>5 different medications during the year preceding DOAC initiation), since these factors have been shown to affect medication adherence in previous studies.[29-33] The definitions of the comorbidities are displayed in Supplementary Table 1.

3 | RESULTS

Altogether, 74 222 patients (mean age 72.7 (SD 10.5) years, 50.8% female) were included in the implementation study cohort and 67 503 patients (mean age 75.3 (SD 8.9) years, 53.6% female) in the persistence study cohort. In both cohorts, patients with higher income were more likely male, had higher education and lower prevalence of cardiovascular comorbidities, dementia, and alcohol use disorders. Similar trends were observed in patients with higher educational level, and additionally, patients with higher education were younger than patients in the lowest educational category (Table 1). Mean duration of persistent DOAC therapy during follow up was 1.4 (SD 1.1) years in the implementation study cohort and 1.3 (SD 1.1) years in the persistence study cohort.

3.1 | Implementation of DOAC therapy

Overall, mean MPR was 0.89 (SD 0.17) and 49 950 (67.3%) patients were adherent to DOACs (MPR ≥0.90) during persistent therapy. The mean MPR, proportion of adherent patients as well as the unadjusted and adjusted odds for adherent DOAC use were all consistently higher among patients in higher income and educational levels (Table 2). The findings were reiterated in the sensitivity analyses covering all DOAC purchases during follow-up (Supplementary Table 2).

3.2 | Persistence of DOAC therapy

A total of 11 856 (17.6%) patients discontinued DOAC therapy during follow-up. Persistence of DOAC use reduced substantially over time (Figure 1). The proportion of patients without therapy discontinuation event still in follow-up at one and two years after DOAC initiation were 81.7% and 69.7%, respectively. Inconsistent differences between income and educational categories were observed in the proportions of patients discontinuing DOAC therapy during entire follow-up, with the highest proportion of discontinued therapies in the highest income and educational categories (Table 3). However, no disparities among income and educational groups were observed in the unadjusted or adjusted incidence rates of therapy discontinuation in the Poisson and Fine-Gray regression models, except for the marginally lower discontinuation rate among patients in the 3rd income quartile, when compared to the lowest income quartile (Table 3). Similarly, in the sensitivity analyses, the overall adjusted cessation rate of DOAC therapy did not differ between income or education categories (Supplementary Table 3).

4 | DISCUSSION

This nationwide cohort study based on pharmacy claims data demonstrated that both income and educational level are independently associated with better implementation of initiated DOAC therapy in patients with incident AF. In contrast, no associations with income or education were observed on the persistence of DOAC therapy.

Previous research assessing the relationship of socioeconomic factors and adherence to DOAC therapy in patients with AF is limited and has demonstrated inconsistent results.[31,34-37] Importantly, most prior works have focused only on a single aspect in medication adherence rather than encompassing both implementation and persistence dimensions of drug utilization. Additionally, these studies have been prone to possible selection, information, and confounding biases owing to use of area-based socioeconomic data, patient samples from only a single level of care, and lack of controlling for possible mortality differences and other confounding factors. Therefore, the results of this large nationwide study covering all patients with AF in Finland considerably increase our understanding of the impact of income and educational attainment on the overall DOAC therapy adherence.

Patients in the highest income and educational categories had 18%–21% higher adjusted odds of sufficient adherence to DOACs (MPR≥0.90) in the therapy implementation phase than patients in the lowest categories, a finding in line with previous reports associating higher socioeconomic status with better therapy implementation in other chronic conditions, although studies on DOAC use in patients with AF have been inconclusive.[37-40] On the other hand, no meaningful difference in persistence of DOAC therapy was observed among income and educational levels, in concordance with a number of observations of similar medication persistence in different socioeconomic categories among patients with and without AF, while reports on worse medication persistence among patients with low socioeconomic status can also be found from previous literature.[34,41-45] However, the large heterogeneity in adherence measures and definitions as well as in the used socioeconomic variables hampers the generalizability and comparability of the results from previous studies. Lower utilization of OAC therapy has been proposed as an underlying mechanism in the observed worse outcomes in patients with AF and low socioeconomic status.[18] Indeed, our findings suggest that inferior implementation of DOAC therapy may contribute to the higher risks among these patients, while differences in treatment persistence are unlikely to play a substantial role in the outcome disparities.

The observed socioeconomic disparities in treatment implementation are likely multifactorial. Importantly, although the costs of DOACs have been largely reimbursed to patients with AF at risk of stroke since 2012 in Finland, DOACs are still significantly more expensive than VKAs, likely hindering their use in patients with low income. Lower levels of health literacy and trust between patients and clinicians may impair understanding of the importance of stroke prevention among patients with lower income or educational background. Additionally, the higher prevalence of mental health

TABLE 1 Descriptive characteristics of the of the study cohorts

	Income quartiles					Educational categories			
	1st (lowest)	2nd	3rd	4th (highest)		s1st (lowest)	2nd	3rd (highest)	
	n = 18 455	*n* = 18 703	*n* = 18 533	*n* = 18 531	*p*-value	*n* = 34 576	*n* = 21 559	*n* = 18 087	*p*-value
Implementation study cohort									
Mean annual income (thousands of euros)	3.9 (5.0)	13.9 (8.4)	25.7 (10.8)	58.7 (24.7)	<.001	16.0 (18.6)	24.1 (21.4)	45.6 (28.1)	<.001
Demographics									
Mean age, years	73.3 (10.4)	73.0 (10.5)	72.4 (10.5)	72.4 (10.4)	<.001	76.2 (9.4)	69.3 (10.6)	70.2 (10.2)	<.001
Female sex	12 257 (66.4)	10 902 (58.3)	8 604 (46.4)	5 944 (32.1)	<.001	19 593 (56.7)	10 523 (48.8)	7 591 (42.0)	<.001
Educational categories				<0.001					
1st	11 573 (62.7)	10 417 (55.7)	7 976 (43.0)	4 610 (24.9)		N/A	N/A	N/A	
2nd	5767 (31.2)	6119 (32.7)	5788 (31.2)	3885 (21.0)		N/A	N/A	N/A	
3rd	1115 (6.0)	2167 (11.6)	4769 (25.7)	10 036 (54.2)		N/A	N/A	N/A	
Income quartiles									<.001
1st	N/A	N/A	N/A	N/A		11 573 (33.5)	5 767 (26.7)	1 115 (6.2)	
2nd	N/A	N/A	N/A	N/A		10 417 (30.1)	6 119 (28.4)	2 167 (12.0)	
3rd	N/A	N/A	N/A	N/A		7 976 (23.1)	5 788 (26.8)	4 769 (26.4)	
4th	N/A	N/A	N/A	N/A		4 610 (13.3)	3 885 (18.0)	10 036 (55.5)	
Comorbidities and risk scores									
Abnormal liver function	55 (0.3)	45 (0.2)	47 (0.3)	43 (0.2)	.60	80 (0.2)	60 (0.3)	50 (0.3)	.46
Abnormal renal function	546 (3.0)	531 (2.8)	483 (2.6)	470 (2.5)	.04	1 135 (3.3)	504 (2.3)	391 (2.2)	<.001
Alcohol use disorder	1008 (5.5)	559 (3.0)	500 (2.7)	419 (2.3)	<.001	1088 (3.1)	879 (4.1)	519 (2.9)	<.001
Any vascular disease	5260 (28.5)	5072 (27.1)	4699 (25.4)	4434 (23.9)	<.001	10 593 (30.6)	5241 (24.3)	3631 (20.1)	<.001
Dementia	722 (3.9)	557 (3.0)	494 (2.7)	435 (2.3)	<.001	1479 (4.3)	428 (2.0)	301 (1.7)	<.001
Diabetes	5064 (27.4)	4575 (24.5)	4226 (22.8)	3827 (20.7)	<.001	8985 (26.9)	5157 (23.9)	3550 (19.6)	<.001
Heart failure	2978 (16.1)	2425 (13.0)	2051 (11.1)	1749 (9.4)	<.001	5291 (15.3)	2477 (11.5)	1435 (7.9)	<.001
Hypertension	15 039 (81.5)	15 030 (80.4)	14 646 (79.0)	14 189 (76.6)	<.001	28 436 (82.2)	16 806 (78.0)	13 662 (75.5)	<.001
Prior bleeding	1773 (9.6)	1757 (9.4)	1813 (9.8)	1739 (9.4)	.51	3583 (10.4)	1979 (9.2)	1520 (8.4)	<.001
Prior ischemic stroke or TIA	3079 (16.7)	2817 (15.1)	2728 (14.7)	2584 (13.9)	<.001	5718 (16.5)	3109 (14.4)	2381 (13.2)	<.001
Prior myocardial infarction	1537 (8.3)	1447 (7.7)	1398 (7.5)	1242 (6.7)	<.001	3034 (8.8)	1528 (7.1)	1062 (5.9)	<.001
Psychiatric disorder	3516 (19.1)	2527 (13.5)	2117 (11.4)	1715 (9.3)	<.001	4757 (13.8)	3150 (14.6)	1968 (10.9)	<.001

(Continues)

TABLE 1 (Continued)

	Income quartiles					Educational categories			
	1st (lowest)	2nd	3rd	4th (highest)		s1st (lowest)	2nd	3rd (highest)	
	n = 18 455	*n* = 18 703	*n* = 18 533	*n* = 18 531	*p*-value	*n* = 34 576	*n* = 21 559	*n* = 18 087	*p*-value
CHA_2DS_2-VASc score	3.8 (1.7)	3.6 (1.7)	3.3 (1.7)	3.1 (1.7)	<.001	3.9 (1.7)	3.1 (1.7)	2.9 (1.6)	<.001
Modified HAS-BLED score	2.7 (1.0)	2.6 (0.9)	2.6 (1.0)	2.6 (1.9)	<.001	2.8 (0.9)	2.5 (1.0)	2.5 (1.0)	<.001
	Income quartiles					**Educational categories**			
	1st (lowest)	**2nd**	**3rd**	**4th (highest)**		**1st (lowest)**	**2nd**	**3rd (highest)**	
	***n* = 16 882**	***n* = 16 915**	***n* = 16 845**	***n* = 16 861**	***p*-value**	***n* = 34 307**	***n* = 18 140**	***n* = 15 056**	***p*-value**
Persistence study cohort									
Mean annual income (thousands of euros)	2.8 (3.6)	11.6 (6.7)	22.8 (9.3)	55.3 (24.3)	<.001	14.9 (17.8)	21.7 (20.9)	43.5 (28.0)	<.001
Demographics									
Mean age, years	75.8 (8.9)	75.6 (8.9)	75.0 (8.9)	75.0 (8.9)	<.001	77.7 (8.3)	72.5 (9.2)	73.4 (8.5)	<.001
Female sex	11 739 (69.5)	10 209 (60.4)	8315 (49.4)	5897 (35.0)	<.001	20 082 (58.5)	9494 (52.3)	6584 (43.7)	<.001
Educational categories					<.001				
1st	11 279 (66.8)	10 278 (60.8)	8141 (48.3)	4609 (27.3)		N/A	N/A	N/A	
2nd	4763 (28.2)	4986 (29.5)	4940 (29.3)	3451 (20.5)		N/A	N/A	N/A	
3rd	840 (5.0)	1651 (9.8)	3764 (22.3)	8801 (52.2)		N/A	N/A	N/A	
Income quartiles									<.001
1st	N/A	N/A	N/A	N/A		11 279 (32.9)	4763 (26.3)	840 (5.6)	
2nd	N/A	N/A	N/A	N/A		10 278 (30.0)	4986 (27.5)	1651 (11.0)	
3rd	N/A	N/A	N/A	N/A		8141 (23.7)	4940 (27.2)	3764 (25.0)	
4th	N/A	N/A	N/A	N/A		4609 (13.4)	3451 (19.0)	8801 (58.5)	
Comorbidities and risk scores									
Abnormal liver function	50 (0.3)	43 (0.3)	45 (0.3)	41 (0.2)	.80	81 (0.2)	52 (0.3)	46 (0.3)	.31
Abnormal renal function	564 (3.3)	575 (3.4)	536 (3.2)	523 (3.1)	.38	1 237 (3.6)	545 (3.0)	416 (2.8)	<.001
Alcohol use disorder	757 (4.5)	502 (3.0)	448 (2.7)	379 (2.2)	<.001	963 (2.8)	677 (3.7)	446 (3.0)	<.001
Any vascular disease	5513 (32.7)	5333 (31.5)	5144 (30.5)	4801 (28.5)	<.001	11 496 (33.5)	5495 (30.3)	3800 (25.2)	<.001
Dementia	783 (4.6)	610 (3.6)	540 (3.2)	499 (3.0)	<.001	1636 (4.8)	457 (2.5)	339 (2.3)	<.001
Diabetes	5256 (31.1)	4910 (29.0)	4697 (27.9)	4254 (25.2)	<.001	9816 (28.6)	5521 (30.4)	3780 (25.1)	<.001

TABLE 1 (Continued)

	Income quartiles					Educational categories			
	1st (lowest)	2nd	3rd	4th (highest)		1st (lowest)	2nd	3rd (highest)	
	n = 16 882	*n* = 16 915	*n* = 16 845	*n* = 16 861	*p*-value	*n* = 34 307	*n* = 18 140	*n* = 15 056	*p*-value
Heart failure	3080 (18.2)	2610 (15.4)	2229 (13.2)	1934 (11.5)	<.001	5768 (16.8)	2580 (14.2)	1505 (10.0)	<.001
Hypertension	14 669 (86.9)	14 677 (86.8)	14 509 (86.1)	14 176 (84.1)	<.001	29 634 (86.4)	15 706 (86.6)	12 691 (84.3)	<.001
Prior bleeding	1770 (10.5)	1757 (10.4)	1844 (10.9)	1802 (10.7)	.35	3779 (11.0)	1918 (10.6)	1476 (9.8)	<.001
Prior ischemic stroke or TIA	3253 (19.3)	3032 (17.9)	3035 (18.0)	2903 (17.2)	<.001	6256 (18.2)	3373 (18.6)	2594 (17.2)	.004
Prior myocardial infarction	1646 (9.8)	1563 (9.2)	1536 (9.1)	1383 (8.2)	<.001	3357 (9.8)	1640 (9.0)	1131 (7.5)	<.001
Psychiatric disorder	3043 (18.0)	2397 (14.2)	2024 (12.0)	1679 (10.0)	<.001	4696 (13.7)	2704 (14.9)	1743 (11.6)	<.001
CHA_2DS_2-VASc score	4.2 (1.4)	4.0 (1.4)	3.8 (1.4)	3.6 (1.4)	<.001	4.2 (1.5)	3.7 (1.4)	3.5 (1.3)	<.001
Modified HAS-BLED score	2.9 (0.9)	2.9 (0.8)	2.8 (0.8)	2.8 (0.8)	<.001	2.9 (0.8)	2.8 (0.9)	2.8 (0.8)	<.001

Note: 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); TIA, transient ischemic attack.

conditions, alcohol use disorders and dementia among patients with lower socioeconomic status may affect medication behavior.[32,33] Yet, these same factors seem not to impact DOAC therapy implementation and persistence to the same extent, since meaningful disparities in medication persistence were not observed.

The main limitations of our study are related to the observational nature of the used administrative data. Hence, the findings reflect associations and not necessarily causation, residual confounding of unmeasured factors cannot be excluded, and information bias may be present due to inaccurate recording of diagnoses and other data. Additionally, some of the used adjusting variables may also have a role as mediators instead of only confounders, especially in the association between educational attainment and adherence. Moreover, our results rely on pharmacy claims and the proportion of drugs truly taken is unknown, and since we lacked data on DOAC prescriptions, we were unable to assess the primary non-adherence to prescribed therapy. Furthermore, clinically indicated treatment gaps are not accounted for in our data, possibly causing downward bias on our adherence estimates. Similarly, we lacked information on the actual patient-level reasons for therapy discontinuation. Moreover, a gold standard to define medication adherence is lacking and there are numerous methods to quantify therapy implementation and persistence, which may influence the results considerably.[46] Nevertheless, our aim was to compare socioeconomic differences in adherence rather than to calculate absolute adherence estimates, and therefore the results are possibly not materially affected by the chosen methodologies. Indeed, the results of the sensitivity analyses were uniform with the results of the main analyses. Likewise, differences in the used socioeconomic variables, for example household vs. individual income, may lead to varying results in health inequality research.[26] However, in our study, income and educational levels both had a similar association on the adherence estimates.

Particular strengths of our study are the large sample size and the comprehensive nature of the used nationwide data, covering all patients with AF in Finland from all levels of care and their individual socioeconomic data as well as all redeemed DOAC prescriptions since DOACs are not sold over the counter without prescription. In addition to the previously reported lower initiation of OAC therapy among AF patients with low socioeconomic status, our results highlight important socioeconomic disparities in the implementation phase of initiated DOAC therapy, and emphasize the need for efforts to ensure adequate quality of stroke prevention for all patients with AF at risk of ischemic stroke.[20]

In conclusion, in this nationwide observational study based on pharmacy claims data, higher income and educational attainment were both independently associated with better implementation of DOAC therapy in patients with incident AF. However, no meaningful disparities in persistence of DOAC therapy was observed among income or educational levels.

DISCLOSURES

Konsta Teppo: none. Jussi Jaakkola: none. Fausto Biancari: none Olli Halminen: none. Jukka Putaala: Dr. Putaala reports personal fees from

TABLE 2 Adherence to direct oral anticoagulant (DOAC) therapy according to income and educational levels

	Mean MPR	Proportion of adherent patients (MPR≥0.90)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Income quartiles	*	*		
1st (lowest)	0.878	64.8%	(Reference)	(Reference)
2nd	0.882	66.3%	1.07 (1.03–1.12)	1.06 (1.01–1.11)
3rd	0.890	68.1%	1.16 (1.11–1.21)	1.09 (1.04–1.14)
4th (highest)	0.897	70.0%	1.27 (1.21–1.32)	1.18 (1.12–1.25)
Educational categories	*	*		
1st (lowest)	0.864	61.0%	(Reference)	(Reference)
2nd	0.904	72.0%	1.64 (1.58–1.70)	1.12 (1.07–1.16)
3rd (highest)	0.911	73.8%	1.80 (1.73–1.87)	1.21 (1.15–1.27)

Note: ORs estimated with binary logistic regression with the following variables included in adjusted analyses: age, sex, calendar year, heart failure, hypertension, diabetes, prior stroke or TIA, vascular disease, prior bleeding, alcohol abuse, renal failure, liver cirrhosis or failure, concomitant use of NSAIDs or antiplatelets, dementia, psychiatric disorder, DOAC dosing, previous VKA use, polypharmacy, income quartiles and education categories.

Abbreviations: CI, confidence interval; MPR, medication possession ratio; OR, odds ratio.

*$p < .001$.

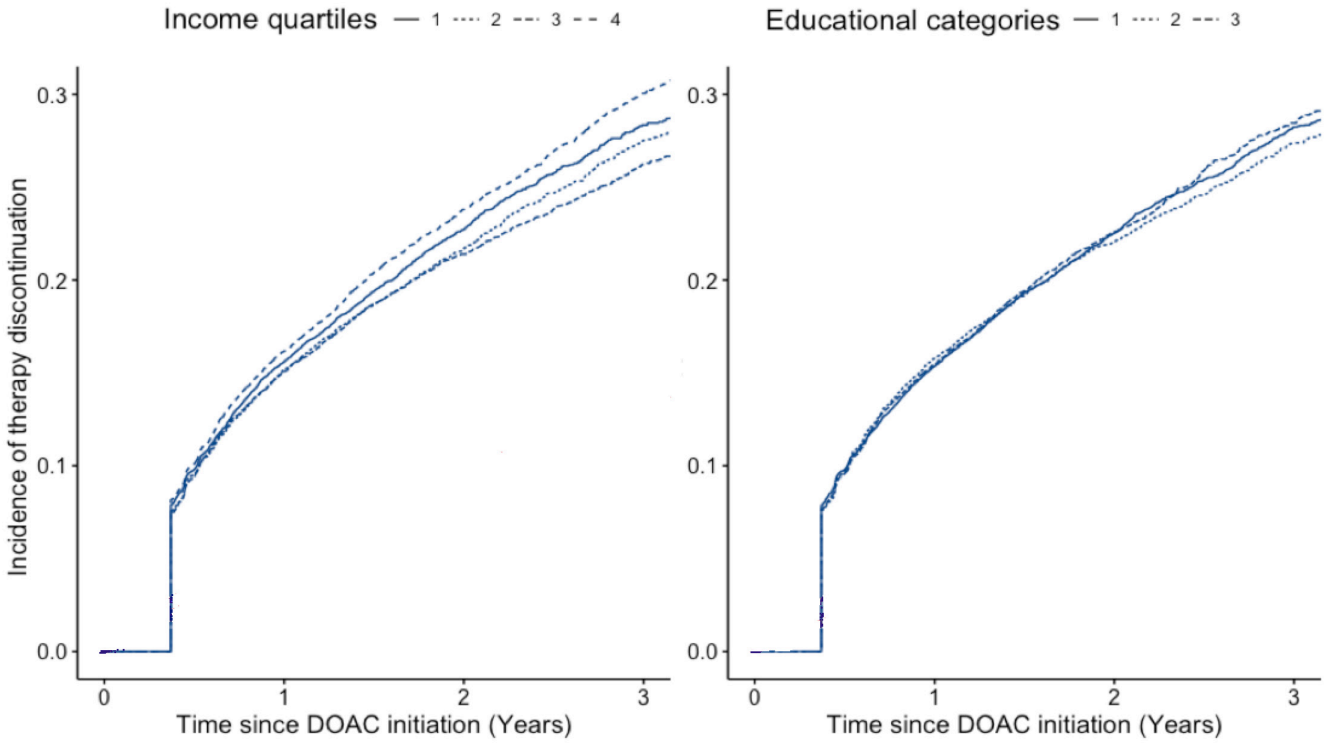

FIGURE 1 Cumulative incidence curve of DOAC therapy discontinuation according to income and educational levels

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TABLE 3 Incidence of direct oral anticoagulant (DOAC) therapy discontinuation according to income and educational levels

	Events	Patient years	Incidence (per patient year)	Unadjusted IRR	Adjusted IRR	Unadjusted SHR	Adjusted SHR
Income quartile*							
1st (lowest)	2 940 (17.4%)	20 863	0.14 (0.14–0.15)	(Reference)	(Reference)	(Reference)	(Reference)
2nd	2 855 (16.9%)	21 487	0.13 (0.13–0.14)	0.94 (0.90–0.99)	0.96 (0.91–1.01)	0.96 (0.91–1.01)	0.96 (0.91–1.01)
3rd	2 832 (16.8%)	21 898	0.13 (0.13–0.13)	0.92 (0.87–0.97)	0.93 (0.88–0.98)	0.94 (0.90–0.99)	0.94 (0.89–0.99)
4th (highest)	3 229 (19.2%)	22 566	0.14 (0.14–0.15)	1.02 (0.97–1.07)	1.01 (0.95–1.07)	1.06 (1.01–1.11)	1.01 (0.95–1.07)
Educational category*							
1st (lowest)	5 962 (17.4%)	42 790	0.14 (0.14–0.14)	(Reference)	(Reference)	(Reference)	(Reference)
2nd	3 109 (17.1%)	23 225	0.13 (0.13–0.14)	0.96 (0.92–1.00)	1.00 (0.95–1.04)	0.99 (0.95–1.03)	1.01 (0.96–1.05)
3rd (highest)	2 785 (18.5%)	20 798	0.13 (0.13–0.14)	0.96 (0.92–1.01)	0.99 (0.94–1.04)	1.01 (0.97–1.06)	1.01 (0.96–1.07)

Note: IRRs estimated by Poisson regression and SHRs by Fine-Gray regression with all-cause death as competing event. Adjusted analyses included the following variables: age, sex, calendar year, heart failure, hypertension, diabetes, prior stroke or TIA, vascular disease, prior bleeding, alcohol abuse, renal failure, liver cirrhosis or failure, concomitant use of NSAIDs or antiplatelets, dementia, psychiatric disorder, DOAC dosing, previous VKA use, polypharmacy, income quartiles and education categories.

Abbreviations: IRR, incidence rate ratio; SHR, subdistribution hazard ratio. 95% confidence intervals in parenthesis.

*$p < .001$.

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AUTHOR CONTRIBUTIONS

Dr Teppo had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: Teppo, Jaakkola, Putaala, Mustonen, Haukka, Airaksinen, Lehto, Acquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript: Teppo, Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: Teppo, Jaakkola, Obtained funding: Lehto, Administrative, technical, or material support: Jaakkola, Halminen, Haukka, Supervision: Jaakkola, Putaala, Mustonen, Haukka, Airaksinen, Lehto.

ETHICS STATEMENT

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 2002.

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).

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SUPPORTING INFORMATION

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