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Mental health conditions and use of rhythm control therapies in patients with atrial fibrillation: a nationwide cohort study

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ABSTRACT

Objectives Mental health conditions (MHCs) have been associated with undertreatment of unrelated medical conditions, but whether patients with MHCs face disparities in receiving rhythm control therapies for atrial fibrillation (AF) is currently unknown. We assessed the hypothesis that MHCs are associated with a lower use of antiarrhythmic therapies (AATs).

Design A nationwide retrospective registry-based cohort study.

Setting The Finnish AntiCoagulation in Atrial Fibrillation cohort included records on all patients with AF in Finland during 2007–2018 identified from nationwide registries covering all levels of care as well as drug purchases. MHCs of interest were diagnosed depression, bipolar disorder, anxiety disorder, schizophrenia and any MHC.

Participants We identified 239 222 patients (mean age 72.6±13.2 years; 49.8% women) with incident AF, in whom the prevalence of any MHC was 19.9%.

Outcomes Primary outcome was use of any AAT, including cardioversion, catheter ablation, and fulfilled antiarrhythmic drug (AAD) prescription.

Results Lower overall use of any AAT emerged in patients with any MHC than in those without MHC (16.9% vs 22.9%, p<0.001). Any MHC, depression, bipolar disorder, anxiety disorder and schizophrenia were all associated with lower incidence of any AAT with adjusted subdistribution HRs of 0.790 (95% CI 0.771 to 0.809), 0.817 (0.796 to 0.838), 0.811 (0.789 to 0.835), 0.807 (0.785 to 0.830) and 0.795 (0.773 to 0.818), respectively. Adjusted rates of AAD, cardioversion and catheter ablation use were lower in all MHC groups compared with patients without MHC. The findings in patients with any MHC were confirmed in propensity score matching analysis.

Conclusions Among patients with AF, a clear disparity exists in AAT use between those with and without MHCs.

Trial registration number ClinicalTrials Identifier: NCT04645537; ENCePP Identifier: EUPAS29845.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is the first study assessing the association of mental health conditions and use of rhythm control therapies in patients with atrial fibrillation (AF).
⇒ Our study covers records of all patients with incident AF in Finland during 2007–2018, including uniquely all levels of care as well as all drug purchases nationwide.
⇒ The main limitation of our study is the retrospective cohort design with its inherent challenges, and the results represent associations and not necessarily causality.
⇒ Our data lacked information on AF subclassifications, AF-related symptoms and the actual reasons for withholding rhythm control therapies.
⇒ Although we were able to adjust our findings for multiple covariates, residual confounding cannot be excluded.

INTRODUCTION

Atrial fibrillation (AF) is the most common arrhythmia affecting up to 4.1% of the population in developed countries.[1 2] Symptoms related to AF range from none to disabling, often impairing daily activities through arrhythmia-related psychological distress and exercise intolerance, and thereby reducing quality of life.[3] Rhythm control therapies or antiarrhythmic therapies (AATs), including antiarrhythmic drugs (AADs), cardioversions and catheter ablations are used in selected patients to reduce symptoms and improve quality of life, and AF-related symptoms are the primary indication for AATs in current guidelines.[3] Recent evidence suggest that they may also reduce the risk of adverse cardiovascular outcomes.[4] The prevalence of mental health conditions (MHCs) in patients with AF has ranged from 18% to 38% in previous reports.[5 6] MHCs have been associated with higher arrhythmia-related symptom burden, lower quality of life and worse outcomes in patients with AF.[6–8] Previous studies have indicated that patients suffering from MHCs are often undertreated for their medical

comorbidities, and MHCs have been associated with poorer prevalence and quality of oral anticoagulation therapy (OAT) in patients with AF.[8–10] However, whether the use of AATs in patients with AF differs between those with and without MHCs is unknown. The present nationwide cohort study thus aimed to investigate the impact of MHCs on the use of AATs in patients with incident AF.

METHODS

Study population

The FinACAF Study (ClinicalTrials Identifier: NCT04645537; ENCePP Identifier: EUPAS29845) is a nationwide retrospective registry-based cohort study covering records of all patients with an AF diagnosis during 2004–2018 in Finland as well as their drug purchases.[2] Patients were identified from three national healthcare registers (hospitalisations and outpatient specialist visits: HILMO; primary healthcare: AvoHILMO; and National Reimbursement Register upheld by Social Insurance Institute: KELA). The inclusion criteria for the cohort were an International Classification of Diseases, Tenth Revision (ICD-10) diagnosis code I48 (including atrial fibrillation and atrial flutter, both referred as AF) recorded between 2004 and 2018. Altogether, 411 387 patients with AF were identified. Patients aged <18 years on the index date and those permanently migrated abroad before 1 January 2019 were excluded. The present substudy was conducted within a cohort of patients with incident AF, established in previous studies of the FinACAF cohort.[10–12] In this cohort, patients with a recorded AF diagnosis during 2004–2006 were excluded because the 2-year medical history was considered too short to exclude the presence of an AF diagnosis before the cohort entry. Additionally, patients who had fulfilled an OAT prescription during 2004–2006 or within a year before the date of first AF diagnosis were excluded since most of them likely had a previous diagnosis of AF. The patient selection process is presented in online supplemental figure 1.

Study protocol

The cohort entry occurred on the date of first recorded AF diagnosis between 1 January 2007 and 31 December 2018. The primary outcome was use of any AAT, including recorded cardioversion (Nordic Classification of Surgical Procedure (NCSP) codes: TPF20, WVA50, WX904), catheter ablation (NCSP codes: TPF44, TPF45, TPF46) and fulfilled AAD prescription(Anatomic Therapeutic Chemical code C01B antiarrhythmics class I and III, plus Anatomic Therapeutic Chemical code C07AA07 sotalol). Catheter ablation procedure codes were renewed in Finland in 2010, and codes prior to 2010 were not specific for AF ablation and therefore not included in our analysis. The outcome was considered to occur on the date of first fulfilled AAD prescription or procedure date after cohort entry, whichever occurred first. The secondary outcomes were cardioversion and catheter ablation procedures and fulfilled AAD prescription individually.

MHCs of interest were depression, anxiety disorder, bipolar disorder, schizophrenia and any MHC. These specific diagnoses were chosen due to their high prevalence and burden in the ageing population of patients with AF.[13] Patients were classified to these groups if they were recorded with the ICD-10 diagnosis code or International Classification of Primary Care, Second Edition (ICPC-2) entry of the condition prior to cohort entry (depression (ICD-10: F32, F33, F34.1; ICPC-2: P76), anxiety disorder (ICD-10: F40-F42, F43.1; ICPC-2: P74), bipolar disorder (ICD-10: F31; ICPC-2: P73), schizophrenia (ICD-10: F20; ICPC-2: P72)). Patients were classified to have any MHC if they had any of these four MHCs and additionally, due to the possible information bias from inaccurate recording of MHC diagnoses, patients who had fulfilled a prescription of an antidepressant, antipsychotic or mood stabilising medication within the year before the index date were classified to have any MHC (Anatomical Therapeutic Chemical codes: N05A, N05BE01, N06A). Medication data were not used to further classify patients to specific conditions.

Patient and public involvement

It was not appropriate or possible to involve patients or the public in the design, or conduct, or reporting, or dissemination plans of our research.

Statistical analysis

Poisson regression was used to determine unadjusted and adjusted incidence rate ratios (IRRs) separately for each AAT and MHC category. Use of AATs might be hindered by mortality occurring during the study period. Therefore, competing risk analyses with the Fine-Gray subdistribution hazard model were performed to estimate the incidence of any AAT considering all-cause mortality as a competing event. Unadjusted and adjusted subdistribution HRs (SHRs) for incidence of any AAT in patients with any MHC as well as in those with different types of MHCs were calculated. In the competing risk analyses, adjustments were made for age, sex, dementia, and alcohol use disorder, and additionally for vascular disease and heart failure as these are important clinical factors in the decision-making of AATs.[3] In addition to these variables, calendar year of AF diagnosis was used in the adjustments of the IRRs. The definitions of the comorbidities are displayed in online supplemental table 1. We additionally analysed the proportions receiving AATs among patients without vascular disease or heart failure, or among those with AF diagnosed under the age of 65, who were therefore more likely eligible for AAT. The χ^2 test was used to compare differences between proportions, and the independent samples t-test to analyse continuous variables.

An imbalance between the study cohorts was observed between a few covariates in the overall series, and therefore an additional propensity score matching was performed to obtain study cohorts balanced for baseline variables. A propensity score was estimated with any MHC as the dependent variable using a non-parsimonious

logistic regression model including age, sex, alcohol abuse, dementia, diabetes, heart failure, hypertension, prior stroke and vascular disease. One-to-one propensity score matching was performed using a caliper width of 0.2 the SD of the logit (ie, 0.1). Standardised differences <0.10 were considered an acceptable imbalance between the matched cohorts. Subsequently, survival analyses with all-cause death as a competing event were performed using the Fine-Gray subdistribution hazard model. Statistical analyses were performed with the IBM SPSS Statistics software (V.27.0, SPSS) and Stata (V.15.1, StataCorp LLC).

RESULTS

A total of 239 222 patients with incident AF were included, of whom 119 045 (49.8%) were women. The mean age at diagnosis was 76.5 years (SD 11.8) in women and 68.9 years (SD 13.5) in men. The overall prevalence of any MHC at cohort entry was 19.9% (47 592 patients). Patients with any MHC were more often women and had higher prevalence of cardiovascular risk factors, dementia and alcohol abuse compared with those with no history of MHC (table 1). Of patients with any MHC, 62.0% had pharmacy claims of antidepressants and 26.7% of antipsychotics prior to cohort entry. OAT was initiated less often in patients with any MHC than among those without MHCs (64.9% vs 73.3%, p<0.001).

Use of any rhythm control therapy

During the study period, the primary outcome, that is, use of any AAT, occurred in 8032 (16.9%) patients with any MHC as compared with 43 901 (22.9%) without MHC (p<0.001) (table 2). Any MHC and all MHC groups were individually associated with lower incidence of any AAT after adjustment for confounding factors both in the Poisson regression model and in the competing risk analysis (tables 2 and 3, figure 1). When analyses were restricted to patients with AF diagnosed under the age of 65 years and without vascular disease or heart failure, any AAT was used in 42.2% of patients without MHC and 33.1% of patients with any MHC (p<0.001). An MHC-related deficit was observed in the use of all AAT modalities across the study period as well as in the use of any AAT in all age groups (figures 2 and 3). The rate of any AAT use was also substantially lower among elderly patients (figure 3). Use of any AAT was lower in patients with any MHC also when analyses were adjusted for use of psychotropic drugs (online supplemental table 2).

Use of AADs

Overall, 21 475 (9.0%) patients received AADs during the follow-up period. The adjusted incidence of AAD use was lower in all MHC groups when compared with patients without MHCs, and a similar trend was observed in all AAD subclasses, except in the use of sotalol (table 2 and online supplemental tables 3 and 4). Among patients aged under 65 years without vascular disease or heart failure, AADs were used in 8130 (19.9%) patients without MHC and 1692 (16.2%) patients with any MHC (p<0.001). Of note, no clinically relevant difference was noted between patients with any MHC and without MHC in the use of rate control drugs, ie, beta-blockers, non-dihydropyridine calcium channel blockers and digoxin (online supplemental tables 3 and 4). Use of AADs was lower in patients with any MHC also when analyses were adjusted for use of psychotropic drugs (online supplemental table 2).

Performance of cardioversions

During the study period, 68 493 cardioversion procedures were performed in 39 313 (16.4%) patients. The adjusted incidence of cardioversion was lower in all MHC groups compared with patients without MHC (table 2). A similar trend was observed in the proportion of patients undergoing more than one cardioversion (online supplemental table 3).

Performance of catheter ablations

A total of 6327 catheter ablation procedures were performed on 5110 (2.1%) patients between 2010 and 2018 when AF-specific procedure codes were recorded. The adjusted catheter ablation IRRs were lower in all MHC groups, although they did not reach statistical significance in patients with depression and bipolar disorder (table 2). Among patients with AF diagnosis under the age of 65 years, 5.3% of patients with any MHC and 7.1% of patients without MHCs underwent an ablation procedure (p<0.001).

Propensity score matching analysis

Propensity score matching provided 47 087 comparable pairs with standardised differences <0.1 for all baseline covariates (online supplemental table 5). Among these propensity score matched pairs, the competing risk analysis demonstrated that any MHC was associated with lower rate of use of any AAT (SHR 0.834; 95% CI 0.809 to 0.859), AADs (SHR 0.867; 95% CI 0.829 to 0.908), cardioversion (SHR 0.805; 95% CI 0.781 to 0.829) and catheter ablation (SHR 0.893; 95% CI 0.804 to 0.993).

DISCUSSION

In this nationwide cohort study, the patients with MHCs and AF were less often treated with AATs compared with those without MHC. After adjusting for confounding factors, lower use of any AAT, AADs, cardioversion and catheter ablation were observed consistently in all MHC categories, although the difference in the use of catheter ablation did not reach statistical significance in patients with depression and bipolar disorder. The lower use of all AAT modalities in patients with MHC persisted throughout the study period.

There are no prior studies investigating the association of MHCs and the use of AATs in patients with AF. Our results may indicate possible underuse of AATs in patients with AF afflicted by MHCs and are in accordance with

Table 1 Baseline characteristics of patients with incident atrial fibrillation according to the presence of mental health conditions (MHCs)

	No MHC	Any MHC	Depression	Bipolar disorder	Anxiety disorder	Schizophrenia
	n=191 675	n=47 547	n=10 920	n=1129	n=4382	n=1560
Mean age, years	72.6 (13.0)	72.8 (14.2)*	69.8 (14.4)*	64.2 (13.0)*	66.2 (16.3)*	69.6 (11.7)*
Female sex	90 754 (47.3)	28 292 (59.5)*	6494 (59.5)*	523 (46.3)	2 675 (61.0)*	823 (52.8)*
Alcohol abuse	5 081 (2.7)	4 354 (9.2)*	1 856 (17.0)*	311 (27.5)*	746 (17.0)*	153 (9.8)*
Dementia	10 576 (5.5)	7335 (15.4)*	1480 (13.6)*	91 (8.1)*	416 (9.5)*	187 (12.0)*
Diabetes	40 143 (20.9)	11 733 (24.7)*	2 962 (27.1)*	360 (31.9)*	1 005 (22.9)*	559 (35.8)*
Dyslipidaemia	91 867 (47.9)	23 854 (50.2)*	5 688 (52.1)*	574 (50.8)	2 136 (48.7)	600 (38.5)*
Heart failure	31 886 (16.6)	9 810 (20.6)*	2 050 (18.8)*	186 (16.5)	702 (16.0)	471 (30.2)*
Hypertension	147 803 (77.1)	38 637 (81.3)*	8944 (81.9)*	892 (79)	3 570 (81.5)*	1 079 (69.2)*
Renal failure or dialysis	3 816 (2.0)	1 197 (2.5)	319 (2.9)	32 (2.8)	117 (2.7)	34 (2.2)
Liver cirrhosis or failure	911 (0.5)	383 (0.8)	132 (1.2)	16 (1.4)	52 (1.2)	10 (0.6)
Prior bleeding	20 625 (10.8)	7 055 (14.8)*	1 874 (17.2)*	185 (16.4)*	740 (16.9)*	228 (14.6)*
Prior stroke	27 463 (14.3)	8 605 (18.1)*	1 938 (17.7)*	196 (17.4)*	693 (15.8)*	231 (14.8)
Vascular disease	48 815 (25.5)	13 598 (28.6)*	3 057 (28.0)*	241 (21.3)*	1 058 (24.1)*	341 (21.9)*
CHA_2DS_2-VASc score	3.4 (1.8)	3.8 (1.9)*	3.6 (1.9)*	3.0 (1.9)*	3.3 (1.9)*	3.4 (1.8)
Modified HAS-BLED score	1.9 (1.0)	2.1 (1.1)*	2.1 (1.1)*	2.0 (1.1)*	2.0 (1.1)*	1.9 (1.0)
Medications before cohort entry						
ADP inhibitors	8 771 (4.6)	2 682 (5.6)*	610 (5.6)*	57 (5.0)*	250 (5.7)*	53 (3.4)*
Dipyridamole	8 968 (4.7)	3 193 (6.7)*	597 (5.5)*	61 (5.4)*	193 (4.4)*	68 (4.4)*
Beta-blockers	94 377 (49.2)	26 005 (54.7)*	5 815 (53.3)*	575 (50.9)*	2 354 (53.7)*	695 (44.6)*
ACE blockers or AT inhibitors	89 601 (46.7)	22 690 (47.5)*	5 123 (46.9)	485 (43.0)*	1 951 (44.5)*	602 (38.6)*
DHP calcium channel blockers	50 983 (26.6)	13 284 (27.9)*	3 018 (27.6)*	277 (24.5)*	1 176 (26.8)	345 (22.1)*
Diuretics	67 031 (35.0)	19 387 (40.8)*	4050 (37.1)*	386 (34.2)*	1 401 (32.0)*	569 (36.5)*
Statins	68 377 (35.7)	17 432 (36.7)*	3 873 (35.5)	410 (36.3)	1 434 (32.7)*	448 (28.7)*
Insulin	10 320 (5.4)	3 504 (7.4)*	896 (8.2)*	111 (9.8)*	257 (5.9)*	168 (10.8)*
Oral diabetes medications	31 064 (16.2)	9 179 (19.3)*	2 325 (21.3)*	283 (25.1)*	763 (17.4)*	460 (29.5)*

Values denote n (%) or mean (SD).
Modified HAS-BLED score, hypertension, abnormal renal or liver function, prior stroke, bleeding history, age >65 years, alcohol abuse (no labile INR or concomitant antiplatelet/non-steroidal anti-inflammatory drugs use, max score 7); Vascular disease includes coronary artery disease and peripheral vascular disease.
Age ≥75 years, diabetes, history of stroke or TIA, vascular disease, age 65–74 years, sex category (women).
*P<0.001 when compared with patients without MHC. Definitions of the comorbidities are presented in the supplementary material. Patients with any MHC also included patients with use of psychotropic drugs.
ADP, Adenosine diphosphate receptor; AT, angiotensin; CHA2DS2-VASc, congestive heart failure, hypertension; DHP, dihydropyridine; TIA, Transient ischemic attack.

previous literature in which it has been demonstrated that patients suffering from MHCs are often undertreated for their somatic disorders and that the rate and quality of OAT are poorer among patients with AF with comorbid MHCs.[8 10 14] Although the primary indication for rhythm control strategy is to reduce AF-related symptoms and improve quality of life, a recent trial also demonstrated that early use of AAT is associated with a lower risk of adverse cardiovascular outcomes.[3 4] Withholding AATs among patients with AF with MHCs may therefore be one underlying mechanism in the previously reported higher risks for adverse outcomes in this patient group.[8]

Table 2 Incidence of antiarrhythmic therapies (AATs) according to the presence of mental health conditions (MHCs)

Outcome	Clinical condition	Events	Proportion of patients with events	P-years (1000 years)	Incidence (per 1000 p-years)	Unadjusted IRR	Adjusted IRR
Any AAT	No MHC	43 901	22.9%	606.88	72.3 (71.7–73.0)	(Reference)	(Reference)
	Any MHC	8032	16.9%	148.40	54.1 (53.0–55.3)	0.748 (0.731–0.766)	0.811 (0.791–0.831)
	Depression	1893	17.3%	29.72	63.7 (60.9–66.6)	0.880 (0.841–0.922)	0.805 (0.768–0.844)
	Bipolar disorder	212	18.8%	3.35	63.3 (55.3–72.4)	0.875 (0.764–1.001)	0.730 (0.637–0.835)
	Anxiety disorder	804	18.4%	11.53	69.8 (65.1–74.8)	0.964 (0.899–1.034)	0.706 (0.658–0.757)
	Schizophrenia	137	8.8%	4.20	32.7 (27.6–38.6)	0.451 (0.382–0.534)	0.408 (0.345–0.482)
AADs	No MHC	17 927	9.4%	725.31	24.7 (24.4–25.1)	(Reference)	(Reference)
	Any MHC	3548	7.5%	168.47	22.3 (21.6–23.0)	0.852 (0.822–0.883)	0.889 (0.857–0.923)
	Depression	801	7.3%	33.50	23.9 (22.3–25.6)	0.967 (0.901–1.038)	0.911 (0.848–0.979)
	Bipolar disorder	83	7.4%	3.84	21.6 (17.5–26.8)	0.876 (0.706–1.086)	0.780 (0.628–0.969)
	Anxiety disorder	347	7.9%	13.04	26.6 (23.9–29.6)	1.076 (0.968–1.197)	0.832 (0.747–0.926)
	Schizophrenia	50	3.2%	4.53	11.0 (8.5–14.6)	0.447 (0.339–0.590)	0.423 (0.320–0.558)
Cardioversion	No MHC	33 446	17.4%	660.17	50.7 (50.1–51.2)	(Reference)	(Reference)
	Any MHC	5867	12.3%	159.28	36.8 (35.9–37.8)	0.727 (0.707–0.748)	0.794 (0.772–0.817)
	Depression	1408	12.9%	31.65	44.5 (42.2–46.9)	0.878 (0.833–0.926)	0.797 (0.755–0.842)
	Bipolar disorder	161	14.3%	3.55	45.4 (38.9–53.0)	0.896 (0.768–1.046)	0.744 (0.637–0.869)
	Anxiety disorder	567	12.9%	12.43	45.6 (42.0–49.5)	0.900 (0.829–0.978)	0.663 (0.610–0.721)
	Schizophrenia	96	6.2%	4.33	22.2 (18.1–27.1)	0.438 (0.358–0.535)	0.391 (0.320–0.477)
Catheter ablation	No MHC	4309	2.2%	799.94	5.4 (5.2–5.5)	(Reference)	(Reference)
	Any MHC	801	1.7%	183.44	4.4 (4.1–4.7)	0.811 (0.752–0.874)	0.837 (0.775–0.904)
	Depression	217	2.0%	36.15	6.0 (5.3–6.9)	1.114 (0.972–1.277)	0.904 (0.787–1.040)
	Bipolar disorder	20	1.8%	4.08	4.9 (3.2–7.6)	0.911 (0.587–1.413)	0.660 (0.425–1.027)
	Anxiety disorder	80	1.8%	14.13	5.7 (4.5–7.0)	1.051 (0.842–1.311)	0.564 (0.451–0.705)
	Schizophrenia	6	0.4%	4.67	1.3 (0.6–2.9)	0.238 (0.107–0.531)	0.215 (0.097–0.480)

95% CIs in parenthesis. IRRs are estimated by Poisson regression and adjusted for age, sex, calendar year of atrial fibrillation diagnosis, dementia, alcohol use disorder, vascular disease and heart failure.
AAD, antiarrhythmic drug; IRR, incidence rate ratio.

Table 3 Ten-year cumulative incidences and risk estimates of any antiarrhythmic therapy use in patients with and without mental health conditions using the Fine-Gray subdistribution hazard model with all-cause death as competing event

Clinical condition	Cumulative incidence (%)	Unadjusted SHR	Adjusted SHR
No MHC	26.5 (26.2–26.7)	(Reference)	(Reference)
Any MHC	19.5 (19.1–19.9)	0.709 (0.692–0.726)	0.790 (0.771–0.809)
Depression	19.4 (19.4–19.9)	0.707 (0.690–0.725)	0.817 (0.796–0.838)
Bipolar disorder	19.1 (18.6–19.6)	0.698 (0.679–0.713)	0.811 (0.789–0.835)
Anxiety disorder	19.3 (18.9–19.8)	0.707 (0.688–0.726)	0.807 (0.785–0.830)
Schizophrenia	18.8 (18.3–19.2)	0.684 (0.666–0.704)	0.795 (0.773–0.818)

95% CIs in parentheses.
SHRs are estimated by Fine-Gray subdistribution hazard model with all-cause death as competing event and adjusted for age, sex, dementia, alcohol use disorder, vascular disease and heart failure.
MHC, mental health condition; SHR, subdistribution HR.

Rate control treatment strategy was chosen in a vast majority of patients, especially among the elderly (table 2, figure 3). Among patients under 65 years without heart disease, the rates of AAT use were substantially higher. AATs are not generally indicated in patients with infrequent, self-limiting AF paroxysms or asymptomatic AF, reducing the need of AAT in our cohort consisting of patients with all types of AF.[3] Additionally, a unique feature of our study was that it also included patients with AF managed solely in the primary care, therefore less likely to receive AATs at all. However, our results reveal an MHC-related deficit in the use of AATs, independent of patients' other clinical characteristics, suggesting disparities in the care of patients with AF with MHCs. Patients with schizophrenia had the lowest rates of AAT use, less than half of the rates in patients without MHCs, a finding corresponding with previous reports on high rates of undertreatment of medical comorbidities in patients with schizophrenia.[9]

Several factors may be associated with the decreased use of AATs among patients with AF with MHCs. Rhythm control treatment decisions are based on symptom severity and the social and cognitive difficulties sometimes associated with MHCs can influence communication between patients and healthcare professionals impairing physicians' understanding of patients AF symptoms and their burden on quality of life.[15] Additionally, the relation of patient's symptoms to AF, especially if non-specific such as shortness of breath or fatigue, may be difficult to distinguish in the presence of MHC and its symptoms. Furthermore, patients with MHCs face barriers in access to healthcare due to the separation of psychiatric and somatic healthcare services, poor socioeconomic conditions prevalent in this patient group, prejudice and inadequate self-care resources, and may therefore be less likely offered more intensive AF treatments. In addition, AADs have several clinically significant interactions with antidepressants and antipsychotics, limiting their use among patients with MHCs.[16] Lower medication compliance associated with MHCs may also play a role in the decreased redemption rate of AADs.[17] Additionally, OAT is a prerequisite to perform elective cardioversions safely and a lower prevalence of OAT has been reported among patients with mentally ill AF.[8] This deficit in the use of OAT may reflect in decreased use of elective cardioversions in patients with AF with MHCs.

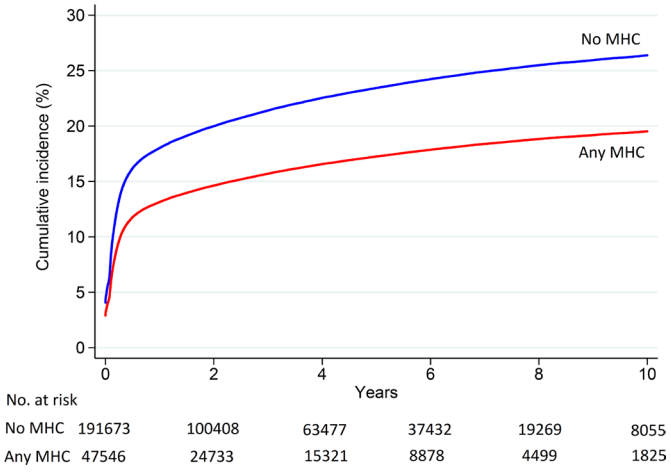

Figure 1 Cumulative ten-year incidence function of the use of any antiarrhythmic therapy with death as competing risk. MHC, mental health condition.

On the other hand, previous literature exhibits observations that might increase the use of AATs in patients with mental illnesses. Depression and anxiety have been shown to increase AF-related symptoms and visits to medical care for AF management, which could increase symptomatic treatment attempts. In addition to the reduction of AF symptom burden, catheter ablation has been shown to decrease also depressive and anxiety symptoms, which may be related to reduction in arrhythmia-related psychological distress and improved exercise tolerance.[18] Depression and anxiety have been reported to increase the risk of AF recurrence after catheter ablation,[19] potentially leading to repeat procedures. Additionally, excessive alcohol consumption, which is associated with MHCs (table 1), has been reported to increase AF paroxysms, total AF burden and AF recurrence after ablation and cardioversion procedures.[20–24]

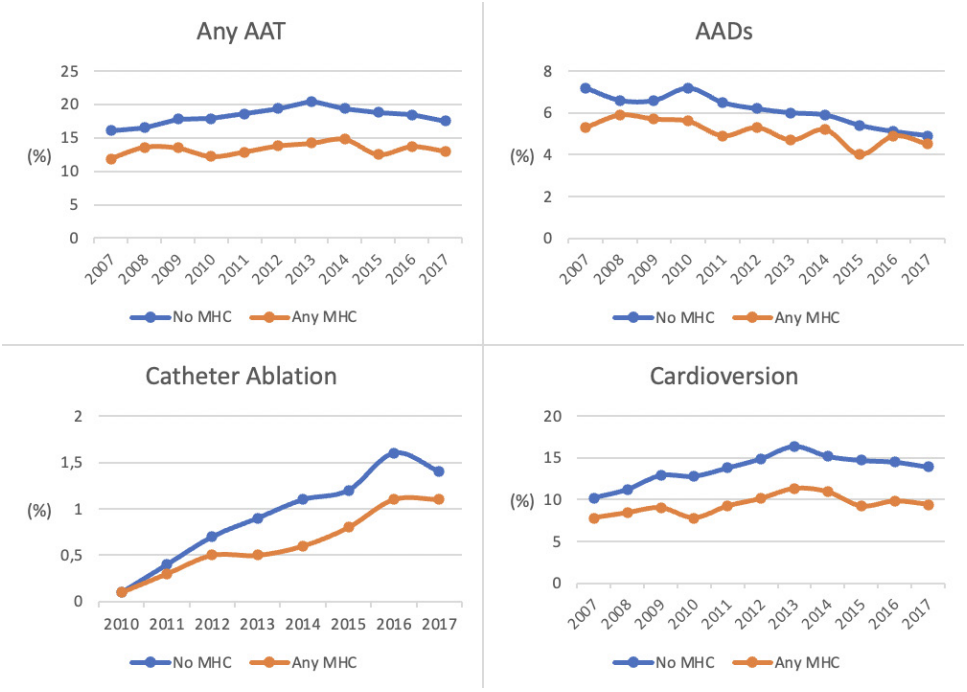

Figure 2 Proportions of patients receiving antiarrhythmic therapies (AATs) by 1-year follow-up according to the year of atrial fibrillation diagnosis. AADs, antiarrhythmic drugs; MHC, mental health condition.

The comprehensive nationwide nature of the present data is the main strength of our study. Patients with AF have been gathered from all available nationwide registers from all levels of care, including uniquely also primary care. These national registries have been well-validated and have sufficient diagnostic accuracy for register based cohort studies.[25] Use of AADs is based on a complete data of redeemed prescriptions, and includes all AAD purchases, since AADs are not sold over the counter without prescription. Furthermore, we were able to adjust our findings with multiple covariates.

The main limitation of our study is the historic cohort design with its inherent challenges; hence, the results represent associations and not necessarily causality. Lifestyle-related factors, except for diagnosed alcohol abuse disorders, were missing in our data. Socioeconomical factors, such as income, were not included in the adjustments, but due to the high reimbursement rates

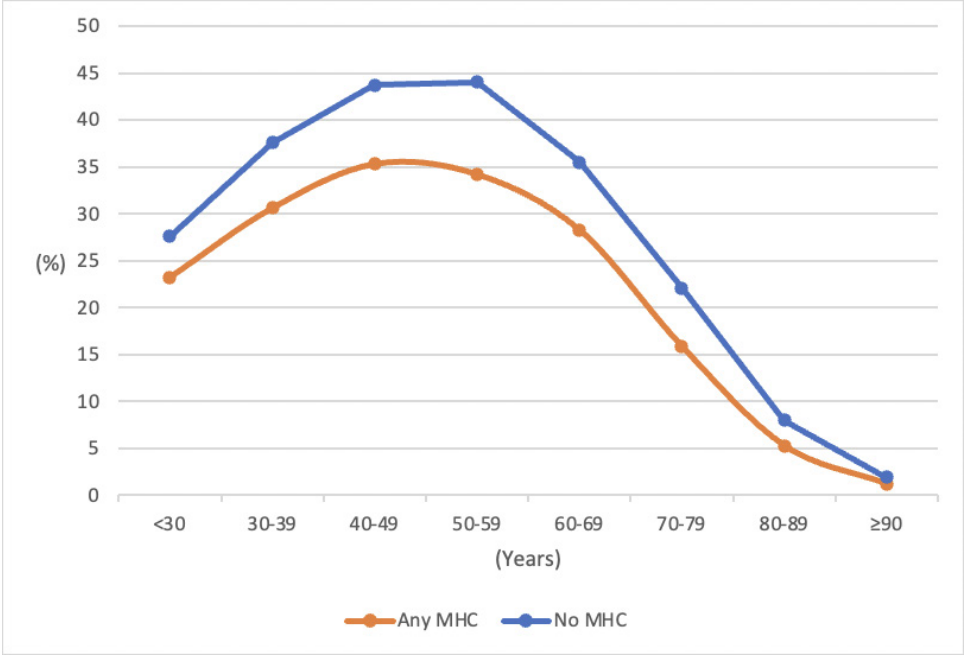

Figure 3 Proportion of patients receiving any antiarrhythmic therapy during follow-up according to the age at atrial fibrillation diagnosis. MHC, mental health condition.

of medical treatment and full coverage of public health insurance in Finland these may not play a critical role in our results. The definitions of MHCs as a single group and individually used in this work are simplifications of complex real-world mental illnesses; however, many similar challenges and barriers in healthcare are experienced by patients within the wide spectrum of MHCs, supporting the used definition of any MHC. Information bias may be present in the classification of MHC categories using recorded codes, but this bias is reduced by using the any MHC variable, which included also purchases of medications used in the treatment of MHCs, although these medications have also marginal use for other indications. Information bias may also be caused by the different diagnostic accuracy of the ICD-10 and ICPC-2 codes. Reliable data on AF ablation procedures were available only from 2010 onward. Additionally, selection bias may be caused in the formation of the study cohort since patients with prior anticoagulant use or emigration during follow-up were excluded. Importantly, we lacked data on AF subclassifications, AF-related symptoms and the actual reasons for withholding AATs. Finally, although we were able to adjust our findings for several covariates, residual confounding cannot be excluded.

Our findings and previous observations on a lower use of OAT in patients with AF with mental illnesses suggest possible inequity in the provided care for this substantially large and vulnerable patient group. To improve the treatment of patients with AF with MHCs, the previously described factors behind lower use of AATs must be tackled. This includes improving physicians' awareness of the higher symptom burden and deficits in the treatment of this patient group and patient education of the symptomatic treatment possibilities as well as lowering their barriers in healthcare access and improving collaboration between somatic and mental health services. Further studies are needed to investigate the factors underlying the lower use of AATs in patients with MHCs, and whether they reflect clinically well-founded reticence or unfounded inequity in the provided care, since these aspects cannot be definitively distinguished from the observational data used in the current study. More information is needed on AF-related symptoms in different MHC groups and on the effects of MHCs on the efficacy of AATs. Further research is required on interventions to improve the treatment of AF patients with MHCs, and on whether the use of AATs improves symptoms or outcomes in these patients.

In conclusion, this nationwide cohort study is the first to demonstrate that MHCs are associated with a lower use of AATs in patients with AF. Further research is needed to better understand the treatment disparities in patients with AF with and without MHCs.

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Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval 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 KELA (138/522/2018), Finnish Institute for Health and Welfare (THL) (THL/2101/5.05.00/2018) and Population Register Center (VRK/1291/2019-3). 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.

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Data availability statement Data may be obtained from a third party and are not publicly available. 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 Centre, and Tax Register).

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Supplementary material

Supplementary Table 1. Definitions of the comorbidities

	ICD-10	ICPC-2	Reimbursement code	ATC code
Hypertension	I10-I15	K85, K86, K87	205	C03A, C03B, C03DB, C03EA, C07A, C08CA, C08D, C09
Dyslipidemia	E78	T93	206	C10
History of heart failure	I50, I11.0, I13.0, I13.2	K77	201	
Diabetes	E10-E14	T89, T90	103, 215	A10
Previous stroke	I63, I64, I69.3-I69.8	K90		
Vascular disease	I20-I25, I65-I66, I67.2, I70	K74, K75, K76, K91, K92	206	
Bleeding history	D50.0, D62, D68.3, I60-I62, I69.0-I69.2, I85.0, I86.4, J94.2, K22.1, K22.3, K22.6, K25.0, K25.2, K25.4, K25.6, K26.0, K26.2, K26.4, K26.6, K27.0, K27.2, K27.4, K27.6, K28.0, K28.2, K28.4, K28.6,			

	K29.0, K62.5, K63.1, K63.3, K92.0-K92.2, N02, R04, R31, R58, S06.2-S06.6, S06.8			
Alcohol abuse	F10			
Dementia	F00-F03, G30			

Abbreviations: ATC, anatomic therapeutic chemical; ICD-10, International Classification of Diseases, Tenth Revision; ICPC-2, International Classification of Primary Care, Second Edition.

Supplementary Table 2. Sensitivity analyses on the use of any AAT and AADs in patients with any MHC adjusted for use of antipsychotic and antidepressive drugs

Outcome	Clinical condition	Adjusted IRR
Any AAT	No MHC	(Reference)
	Any MHC	0.830 (0.806-0.854)
AADs	No MHC	(Reference)
	Any MHC	0.878 (0.840-0.917)

Abbreviations: AAD, antiarrhythmic drug; AAT, antiarrhythmic therapy; IRR, incidence rate ratio; MHC, mental health condition. 95% confidence intervals in parenthesis. IRRs are estimated by Poisson regression and adjusted for age, sex, calendar year of AF diagnosis, dementia, alcohol use disorder, vascular disease, heart failure and the use of antipsychotic and antidepressive drugs.

Supplementary Table 3. Use of rate control drugs, AADs and repeat AAT procedures during follow-up

	No MHC	Any MHC	Depression	Bipolar disorder	Anxiety disorder	Schizophrenia
Beta-blockers	156 945 (81.9%)	37 792 (79.5%)	8 729 (79.9%)	927 (82.1%)	3 552 (81.1%)	1 143 (73.3%)
Digoxin	32 564 (17.0%)	8 215 (17.3%)	1 495 (13.7%)	151 (13.4%)	496 (11.3%)	271 (17.4%)
NDCB	6 690 (3.5%)	1 717 (3.6%)	356 (3.3%)	30 (2.7%)	145 (3.3%)	37 (2.4%)
Amiodarone	5 623 (2.9%)	1 041 (2.2%)	270 (2.5%)	32 (2.8%)	110 (2.5%)	38 (2.4%)
Dronedarone	902 (0.5%)	160 (0.3%)	30 (0.3%)	3 (0.3%)	11 (0.3%)	0 (0.0%)
Flecainide	9 461 (4.9%)	1 902 (4.0%)	412 (3.8%)	36 (3.2%)	184 (4.2%)	10 (0.6%)
Sotalol	1 706 (0.9%)	391 (0.8%)	81 (0.7%)	11 (1.0%)	38 (0.9%)	2 (0.1%)
Ablations >1	857 (0.4%)	152 (0.3%)	36 (0.3%)	0 (0%)	11 (0.3%)	0 (0%)
Cardioversions > 1	10 666 (5.6%)	1 810 (3.8%)	414 (3.8%)	42 (3.7%)	161 (3.7%)	13 (0.8%)

Abbreviations: NDCB, Non-dihydropyridine calcium channel blockers; MHC, Mental health condition

Supplementary Table 4. Odds ratios of rate and rhythm control drug use during follow-up in patients with any MHC compared with patients without MHCs.

	Unadjusted OR	**Adjusted OR**
Beta-blockers	0.86 (0.84-0.88)	0.94 (0.92-0.97)
Digoxin	1.02 (0.99-1.05)	0.99 (0.96-1.02)
NDCB	1.04 (0.98-1.09)	1.06 (1.00-1.12)
Amiodarone	0.74 (0.69-0.79)	0.81 (0.75-0.86)
Dronedarone	0.71 (0.60-0.85)	0.80 (0.68-0.95)
Flecainide	0.80 (0.76-0.84)	0.88 (0.84-0.93)
Sotalol	0.92 (0.83-1.03)	1.08 (0.97-1.21)

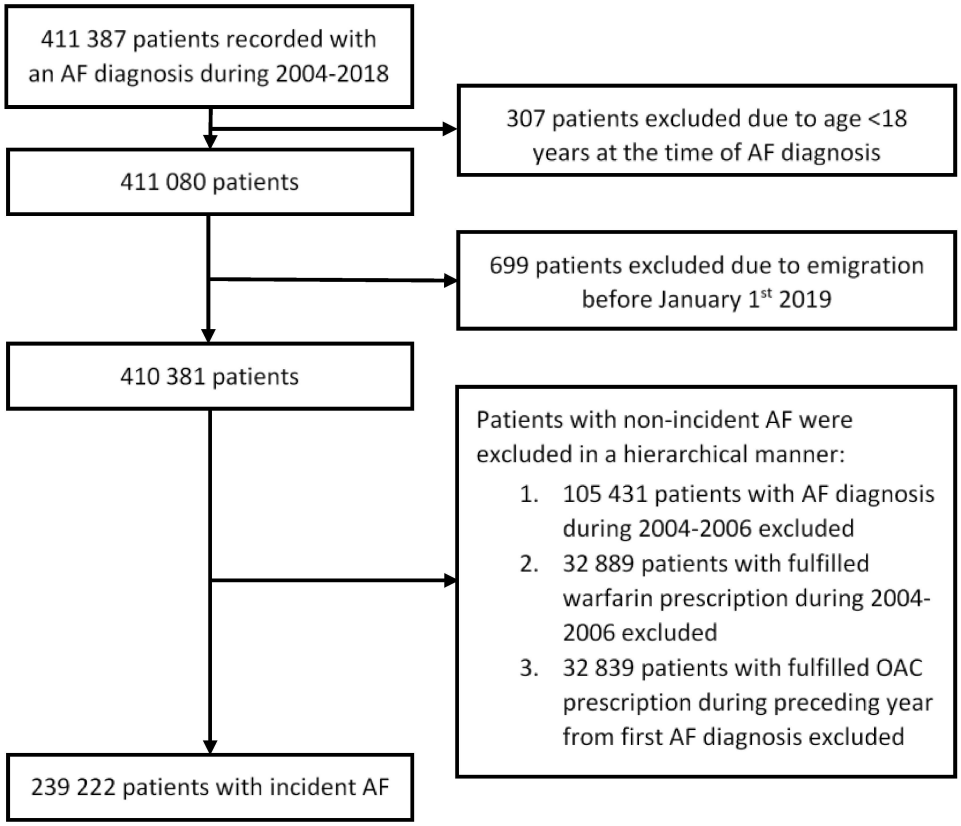
Abbreviations: NDCB, Non-dihydropyridine calcium channel blockers; MHC, Mental health condition; OR, odds ratio. ORs estimated with binary logistic regression and adjusted for age, sex, dementia, alcohol use disorder, vascular disease, and heart failure.

Supplementary Table 5. Baseline characteristics of patients with incident AF according to the presence of any MHCs before and after propensity score matching.

	Unmatched patients			Propensity score matched pairs		
	No MHC	Any MHC	Standardized differences	No MHC	Any MHC	Standardized differences
	n=191 675	n=47 547		n=47 087	n=47 087	
Age, years (SD)	72.6 (13.0)	72.8 (14.2)	0.016	73.2 (13.6)	72.9 (14.2)	0.020
Female sex	90 754 (47.3%)	28292 (59.5%)	0.246	28 423 (60.4%)	28 002 (59.5%)	0.018
Alcohol abuse	5 081 (2.7%)	4 354 (9.2%)	0.279	3876 (8.2%)	3 902 (8.3%)	0.002
Dementia	10 576 (5.5%)	7335 (15.4%)	0.328	7 099 (15.1%)	7 003 (14.9%)	0.005
Diabetes	40 143 (20.9%)	11 733 (24.7%)	0.089	11 422 (24.3%)	11 542 (24.5%)	0.006
Heart Failure	31 886 (16.6%)	9 810 (20.6%)	0.103	9 396 (20.0%)	9 671 (20.5%)	0.015
Hypertension	147 803 (77.1%)	38637 (81.3%)	0.102	38 631 (82.0%)	38240 (81.2%)	0.021
Prior stroke	27 463 (14.3%)	8 605 (18.1%)	0.102	8 362 (17.8%)	8 456 (18.0%)	0.005
Vascular disease	48 815 (25.5%)	13 598 (28.6%)	0.071	13 447 (28.6%)	13 442 (28.5%)	0.000
CHA_2DS_2-VASc score (SD)	3.4 (1.8)	3.8 (1.9)	0.191	3.8 (1.9)	3.8 (1.9)	0.011

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); MHC, mental health condition; SD, standard deviation.

Supplementary Figure 1. Flow-chart of the study patient selection process



Abbreviations: AF, atrial fibrillation