Received: 22 December 2021 | Revised: 16 March 2022 | Accepted: 19 March 2022

DOI: 10.1111/bcp.15337

ORIGINAL ARTICLE

Disparities in oral anticoagulation initiation in patients with schizophrenia and atrial fibrillation: A nationwide cohort study

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Aims: Schizophrenia is associated with poor anticoagulation control and clinical prognosis in patients with atrial fibrillation (AF). Little is known about initiation of oral anticoagulation therapy (OAC) in this patient population.

Methods: In the nationwide Danish health registries, we identified all patients with incident AF and schizophrenia with indication for OAC treatment. Patients with schizophrenia ($n = 673$) were matched 1:5 on sex, age, stroke risk score, and calendar-period to incident AF patients without schizophrenia. We calculated absolute risk and risk difference (RD) of OAC initiation, adjusting for stroke and bleeding risk factors. Analyses were stratified by calendar period (2000–2011 and 2012–2018) to account for changes after the introduction of non-vitamin K OACs (NOAC).

Results: Among patients with schizophrenia (mean age 69.5 years, 50.3% females), 33.7% initiated OAC within the first year after AF diagnosis, compared with 54.4% of patients without schizophrenia, corresponding to an adjusted RD of −20.7 (95% confidence interval [CI]: −24.7 to −16.7). OAC initiation increased over time regardless of schizophrenia status. During 2000–2011, 18.3% of patients with schizophrenia and 42.9% without schizophrenia initiated OAC (adjusted RD −23.6%, 95% CI −28.8 to −18.6). During 2012–2018, this was 48.5% and 65.7%, respectively (adjusted RD −14.4%, 95% CI −20.4 to −8.4).

Conclusion: Initiation of OAC was substantially lower among patients with AF and schizophrenia compared with matched AF peers. These findings accentuate the importance of close attention to disparities in initiation of OAC treatment, and potential missed opportunities for prevention of disabling strokes in AF patients with schizophrenia.

KEYWORDS
anticoagulants, atrial fibrillation, schizophrenia, thrombosis

1 | INTRODUCTION

Cardiovascular diseases are highly prevalent and a predominant cause of a 10–20 year shorter life expectancy in patients with schizophrenia compared with the general population.[1] Atrial fibrillation (AF) is the most common cardiac arrhythmia and increases the risk of stroke by up to five-fold.[2] Prior studies have shown an increased risk of stroke and higher mortality following a thromboembolic event in AF patients with schizophrenia compared to AF patients without schizophrenia.[3,4]

Oral anticoagulation therapy (OACs) reduces the incidence of thromboembolic events and death among patients with AF.[5] Despite evidence of a benefit in patients with schizophrenia, clinicians may be concerned about the effectiveness and safety of anticoagulation in this clinically complex patient group.[6] Prior studies have shown that AF patients with schizophrenia have worse anticoagulation control when treated with warfarin, and are at increased risk of major bleeding than patients without schizophrenia.[3,7–9] Nevertheless, non-initiation of OAC treatment could be a missed opportunity to prevent disabling strokes in patients with schizophrenia who could be safely treated. Previous studies have indicated treatment disparities in patients with severe mental disorders, where AF patients who are eligible for anticoagulation are less likely to receive treatment.[6,9] Since these studies were confined to experienced OAC users, they did not investigate treatment initiation. Moreover, it is unknown whether the introduction of non-vitamin K antagonist OACs (NOAC), which have the advantage of a more simple dosing strategy, have reduced treatment disparities.

The aim of this study was to examine OAC initiation in patients with schizophrenia diagnosed with incident AF. We tested the hypothesis that AF patients with schizophrenia, and a treatment indication for stroke prevention, would be less likely to initiate OAC treatment than AF patients without schizophrenia.

What is already known about this subject

- Atrial fibrillation is a common cardiac arrhythmia in patients with schizophrenia and has been shown to confer an increased risk of stroke and higher mortality than in atrial fibrillation patients without schizophrenia.
- Previous studies have indicated treatment disparities in patients with severe mental disorders, where atrial fibrillation patients who are eligible for anticoagulation are less likely to receive treatment.
- These studies have been confined to experienced anticoagulation users, and little is known about initiation of anticoagulation therapy in patients with schizophrenia.

What this study adds

- This nationwide study, which include data on all Danish patients with schizophrenia diagnosed with incident atrial fibrillation, revealed treatment initiation of anticoagulation therapy in patients with schizophrenia compared with atrial fibrillation patients without schizophrenia.
- These findings extend prior studies by focusing on treatment initiation in anticoagulation naïve incident atrial fibrillation patients, who had a clear recommendation for anticoagulant treatment.
- Despite improved anticoagulation initiation over time, substantial disparities remained which draw attention to potential missed opportunities for prevention of disabling strokes in patients with schizophrenia.

2 | METHODS

2.1 | Registry data sources

This cohort study linked three nationwide Danish registries: (1) the National Patient Register, which contains detailed information on more than 99% of all hospital admissions discharge with diagnoses coded according to the International Classification of Diseases (ICD) including psychiatric in-patient admissions[10]; (2) the National Prescription Registry, which holds information on all redeemed prescriptions by Danish residents since 1995, including Anatomic Therapeutic Chemical classification code, dispensing date and package details for every prescription purchase[11]; and (3) the Danish Civil Registration System, which holds information on sex, date of birth, death and emigration status of all Danish residents.[12] Data were linked using the unique civil registration number assigned to all Danish residents at birth or immigration, allowing a true population-based study covering all 5.6 million Danish inhabitants.[13] Table S1 in the Supporting Information provides information on codes used in the study.

The study was conducted in compliance with the General Data Protection Regulation, and is part of North Denmark Region's record of processing activities (File No. 2015-57-0001). Other approvals were not necessary according to Danish legislation.

2.2 | Study population

We identified all patients discharged with a first-time hospital diagnosis of non-valvular AF who had an indication for OAC, between 1 January 2000 and 31 December 2017. Non-valvular AF was defined as the presence of AF, with no prior record of mitral stenosis or mechanical heart valve replacement. The date of hospital discharge for AF was defined as the index date (baseline). Treatment indication for OAC was defined according to the recommended stroke risk stratification guiding OAC treatment decisions in the study period. Thus, for patients with an AF diagnosis between 2000 and 2011, OAC treatment indication was defined by a $CHADS_2$ stroke risk score of

≥1.[14] For patients with an AF diagnosis between 2012 and 2017, OAC treatment indication was defined by a CHA_2DS_2-VASc stroke risk score of ≥1 for men and ≥2 for women.[15] The $CHADS_2$ stroke risk score was calculated using combined baseline information on congestive heart failure, hypertension, age ≥75, diabetes mellitus, prior stroke or transient ischaemic attack.[14] The CHA_2DS_2-VASc stroke risk score was calculated using combined baseline information on congestive heart failure, hypertension, age ≥75, diabetes mellitus, prior stroke, transient ischaemic attack or thromboembolism, vascular disease age 65–74 years and female sex (see detailed score definitions in Table S2 in the Supporting Information).[15] We excluded patients who had not been resident in Denmark for at least 1 year before the AF discharge diagnosis to ensure clinical record history. Since we focused on initiation of OAC treatment, we excluded all patients with baseline use of either vitamin K antagonists (VKA) or NOAC, as described previously.[16]

In the study population, we identified all patients with an inpatient or outpatient diagnosis of schizophrenia derived from hospital diagnosis record in the National Patient Register. To control for confounding for treatment initiation, we used a risk-set sampling approach with replacement to select a 5:1 control population of schizophrenia-free patients in the AF population matched on age, sex, stroke risk and calendar-period of diagnosis (2000–2005, 2006–2011, 2012–2017). Stroke risk was assessed by $CHADS_2$ scores (grouped as 1, 2 and ≥3) for patients diagnosed between 2000 and 2011, and CHA_2DS_2-VASc (1, 2 and ≥3) for patients diagnosed between 2012 and 2017.

2.3 | Baseline characteristics and comorbidities

Baseline comorbidity and medication usage were ascertained from primary or secondary hospital discharge diagnoses and/or prescription information. Comorbidity information included cardiovascular and metabolic diseases as well as lifestyle-related diseases. Concomitant medication use was based on redeemed prescriptions within 365 days before the index date. We combined baseline information into the CHA_2DS_2-VASc score as described above to summarize perceived stroke risk at baseline.[15] Likewise, we summarized perceived bleeding risk at baseline according to the HAS-BLED score combining information on hypertension, abnormal renal or liver function, stroke or thromboembolism, bleeding history, labile international normalized ratio (INR) (not included because of data unavailability), elderly (age > 65 years), drug consumption/alcohol excess (see Table S2 in the Supporting Information for details).[17]

2.4 | Outcomes

We investigated initiation of OAC therapy including VKA (warfarin and phenprocoumon) and NOAC (dabigatran, rivaroxaban, apixaban and edoxaban), defining treatment initiation by the first redeemed OAC prescription after AF diagnosis using records in the Danish National Prescription registry. To assess potential non-prescription because of short remaining life expectancy, we also included all-cause mortality. Finally, in an exploratory, hypothesis-generating analysis, we investigated 1-year rates of ischaemic stroke.

2.5 | Statistical analysis

Patients were followed for a maximum of 1 year after their AF discharge diagnosis. Follow-up was administratively censored at the outcome of interest, death, migration or study end (31 December 2018), whichever came first. Descriptive characteristics of the study population were presented by means and standard deviations for continuous measures, counts and percentages for categorical measures. Cumulative incidence functions (by means of the Aalen-Johansen estimator), assuming death as a competing risk, were used to depict OAC initiation during follow-up. We used pseudo-value regression with an identity log-link function on a risk difference scale to compute the absolute 1-year risk of OAC initiation comparing AF patients with and without schizophrenia. To access to what extent the observed risk differences could be explained by stroke or bleeding risk, we conducted multivariate regression of pseudo-values adjusting for the effect of the individual components of the baseline CHA_2DS_2-VASc and HAS-BLED scores. We excluded age in the CHA_2DS_2-VASc and HAS-BLED scores, as these were included as matching factors and was balanced between AF patients with and without schizophrenia. The analyses were repeated with stratification according to calendar time before and after the introduction of NOAC in Denmark (2000–2011 and 2012–2018), and according to CHA_2DS_2-VASc score; a chi-square test was performed to statistically quantify temporal trends. In a supplementary, hypothesis-generating analysis, we calculated rates of ischaemic stroke per 100 person-years by time periods (2000–2005, 2006–2011, 2012–2018) and schizophrenia status.

To assess the robustness of our methodological approach, we conducted a sensitivity analysis restricting the study population to patients with a primary diagnosis of AF to ensure that AF was the primary cause of hospital admission to increase the likelihood of treatment indication.

All analyses were performed using STATA/MP (v. 15.1), and a *P*-value of .05 was chosen as the level of statistical significance.

3 | RESULTS

We identified 238 714 patients with incident AF, who had an indication for OAC treatment at the time of AF diagnosis between 2000 and 2017. After exclusions, the study population comprised 192 434 AF patients of whom 662 had schizophrenia (Figure S1 in the Supporting Information provides a flowchart of the study population). The mean age was 69.5 years, and the mean CHA_2DS_2-VASc score was 3.1 (Table 1). AF patients with schizophrenia had a higher prevalence of heart failure (35.0% *vs.* 28.5%)

TABLE 1 Characteristics of patients with incident atrial fibrillation according to presence of schizophrenia, 2000–2017

Characteristic	AF patients with schizophrenia ($n = 662$)	Matched AF patients without schizophrenia ($n = 3265$)
Sex (females), % (*n*)	50.3 (333)	50.5 (1649)
Age, mean (SD)	69.5 (11.6)	69.6 (11.5)
Time period (2000–2011), % (*n*)	51.4 (340)	51.2 (1671)
Hospital days, mean (SD)	12.0 (16.3)	10.4 (17.1)
CHA_2DS_2-VASc score, mean (SD)	3.1 (1.5)	3.1 (1.5)
HAS-BLED score, mean (SD)	2.2 (1.2)	2.2 (1.1)
Comorbidity, % (*n*)		
Heart failure	35.0 (232)	28.5 (929)
Hypertension	34.5 (232)	51.6 (1738)
Diabetes	31.4 (228)	18.9 (618)
Ischaemic stroke	18.9 (125)	18.9 (617)
Myocardial infarction	10.7 (71)	13.5 (441)
Peripheral arterial disease	9.1 (60)	8.5 (277)
Prior venous thromboembolism	6.6 (44)	5.1 (168)
Cancer	13.7 (91)	16.3 (533)
Prior bleeding event	16.3 (108)	14.5 (473)
Alcohol-related disease	21.9 (145)	6.8 (221)
Concomitant medication[a], *n* (%)		
Aspirin	35.8 (237)	37.9 (1236)
Thienopyridines	7.9 (52)	7.9 (257)
β-blocker	23.1 (153)	35.9 (1172)
Statin	26.0 (172)	33.5 (1094)
NSAID	22.1 (146)	25.5 (832)
Renin-angiotensin inhibitors	32.0 (212)	46.2 (1509)
Non-loop diuretics	31.7 (210)	40.4 (1320)
Loop diuretics	39.0 (258)	23.4 (764)
Antipsychotics, lithium and anxiolytics/ hypnotics	85.2 (564)	25.0 (816)
Antidepressants	33.8 (224)	15.5 (505)
Antiepileptics	21.0 (139)	5.1 (167)

SD: standard deviation, AF: atrial fibrillation.
[a]Redeemed prescription up to 365 days before index date.

and diabetes (31.4% *vs.* 18.9%), but lower prevalence of hypertension (34.5% *vs.* 51.6%). The mean HAS-BLED score was 2.2 in both groups, but alcohol-related diseases were more prevalent in patients with schizophrenia (21.9% *vs.* 6.8% in patients without schizophrenia).

The cumulative incidence curves revealed that OAC treatment initiation was substantially lower in AF patients with schizophrenia than in matched AF patients without schizophrenia (Figure 1). After 1 year, 33.7% of AF patients with schizophrenia had redeemed an OAC prescription compared with 54.4% of patients with AF without schizophrenia. This corresponded to a crude risk difference of −20.7 (95% CI: −24.7 to −16.7). The risk difference was similar after adjusting for stroke and bleeding risk factors −19.4 (95% CI: −23.6 to −15.3) (Table 2).

OAC initiation was lower for AF patients with schizophrenia *vs.* patients without across categories of the CHA_2DS_2-VASc score (Table 2). Stratification by time-period showed higher OAC initiation over time, particularly among patients with schizophrenia: before the introduction of NOACs, 18.3% of AF patients with schizophrenia and 42.9% of AF patients without schizophrenia redeemed an OAC prescription within 1 year (adjusted RD −24.6%, 95% CI −29.5 to −19.9). In the period after NOAC introduction, this increased to 48.5% and 65.7%, respectively (adjusted RD −14.4%, 95% CI −20.4 to −8.4) (Table 2). Between 2012 and 2018, NOAC accounted for 77.1% of the redeemed prescriptions in patients with AF with schizophrenia, and 67.3% in matched AF patients without schizophrenia. OAC initiation increased after introduction of NOACs regardless of schizophrenia status and CHA_2DS_2-VASc score, though OAC

initiation remained significantly lower among AF patients with schizophrenia across categories of the CHA_2DS_2-VASc score (Figure 2). Restricting the analyses to patients with a primary diagnosis of AF led to similar risk differences as the main analysis, but higher crude OAC initiation estimates in patients with and without schizophrenia (Table S3 in the Supporting Information).

The cumulative incidence proportion of all-cause mortality is shown in Figure S2 in the Supporting Information. At 1-year follow-up, all-cause mortality was 33.8% in AF patients with schizophrenia and 15.4% in AF patients without schizophrenia. Figure 3 shows the temporal trends of OAC initiation and 1-year rates of ischaemic stroke and all-cause mortality according to schizophrenia status. There was a trend for increasing OAC initiation during the three time-periods, which was evident regardless of schizophrenia status (*P*-value < .001). Concurrent with increasing OAC initiation over time, rates of ischaemic stroke decreased from 9.2 per 100 person-years in 2000–2005 to 7.9 in 2015–2017 among patients without schizophrenia, and fluctuated around 6.8–8.0 among patient with schizophrenia (Table S4 in the Supporting Information). Rates of all-cause mortality decreased from 52.9 per 100 person-years to 40.1 in patients with schizophrenia, and from 20.3 to 15.4 in those without.

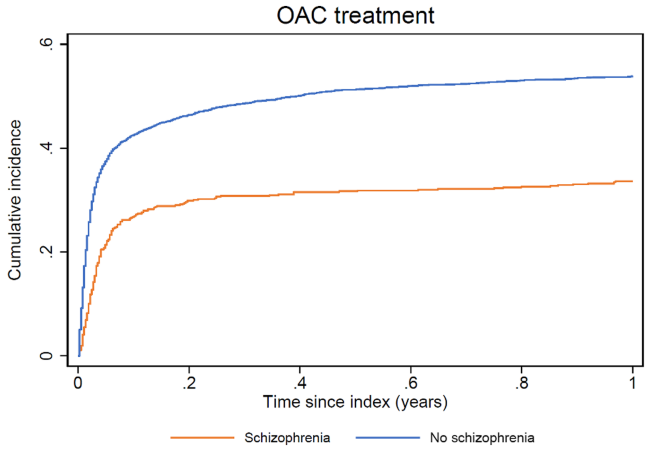

FIGURE 1 Cumulative incidence of oral anticoagulation therapy in patients with atrial fibrillation with and without schizophrenia

4 | DISCUSSION

Our nationwide cohort study revealed that patients with schizophrenia and treatment indication for stroke prevention were less likely to initiate OAC treatment following an AF diagnosis than matched AF patients without schizophrenia. This association remained unchanged after controlling for differences in stroke and bleeding risk factors. Second, OAC initiation increased following the introduction of NOACs, but remained lower in AF patients with schizophrenia *vs.* matched patients without. However, despite increase in OAC initiation over time among AF patients with schizophrenia, rates of ischaemic stroke remained unchanged over time.

Our findings are consistent with the emerging literature documenting lower-intensity care provided for patients with schizophrenia for a range of cardiovascular diseases.[6,9,18–20] Prior studies have shown that warfarin-experienced AF patients with schizophrenia are less likely to receive OAC therapy, despite a perceived high risk of stroke. In a cohort study of 12 190 experienced AF patients with a mental health condition eligible for warfarin, Schmitt et al. found that the subgroup of 575 patients with psychotic disorders were significantly less likely to receive warfarin treatment than patients without a mental health condition (OR 0.77, 95% CI: 0.65–0.90).[6] Similarly, Walker et al. found that 48.5% of warfarin-eligible AF patients with a mental health condition did not receive warfarin treatment compared to only 27.3% of patients without a mental health condition.[9] Our

TABLE 2 Oral anticoagulation therapy initiation in arterial fibrillation patients with schizophrenia and matched atrial fibrillation patients without schizophrenia at one-year follow-up

	Oral anticoagulation therapy (%)		Unadjusted risk difference	Adjusted risk difference[a]
	Schizophrenia	No schizophrenia	Schizophrenia *vs.* no schizophrenia (95% CI)	Schizophrenia *vs.* no schizophrenia (95% CI)
Overall	33.7	54.4	-20.7 (−24.7 to −16.7)	−19.4 (−23.6 to −15.3)
2000–2011	18.3	42.9	−24.6 (−29.5 to −19.8)	−23.6 (−28.8 to −18.6)
2012–2018	48.5	65.7	−17.2 (−23.0 to −11.4)	−14.4 (−20.4 to −8.4)
CHA_2DS_2-VASc				
Score 1	38.4	60.1	−21.7 (−32.3 to −11.1)	−17.2 (−28.1 to −6.3)
Score 2	31.4	57.5	−26.2 (−34.3 to −18.0)	−23.7 (−32.3 to −15.2)
Score ≥3	33.5	52.0	−18.5 (−23.6 to −13.4)	−17.8 (−23.0 to −12.5)

[a]Adjusted for individual factors included in the CHA_2DS_2-VASc; congestive heart failure; hypertension; diabetes mellitus; prior stroke, transient ischaemic attack or thromboembolism; vascular disease[15] (age and sex where applied as matching factors in the study design); HAS-BLED; hypertension; abnormal renal or liver function; stroke or thromboembolism; bleeding history; labile international normalized ratio (not included because of data unavailability); drug consumption/alcohol excess.[17]

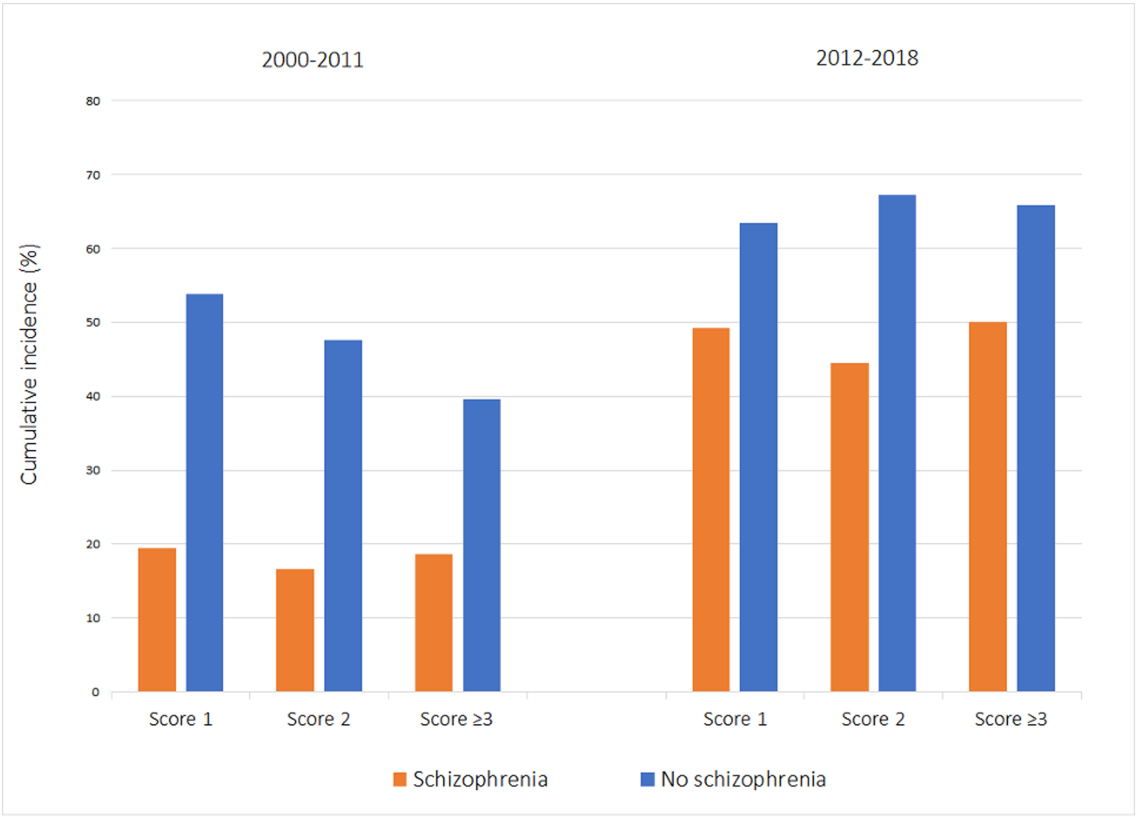

FIGURE 2 Oral anticoagulation therapy according to CHA_2DS_2-VASc score and time period [a] Individual components of the CHA_2DS_2-VASc included in the adjustment: congestive heart failure; hypertension; diabetes mellitus; prior stroke, transient ischaemic attack or thromboembolism; vascular disease (age and sex were applied as matching factors in the study design).[15]

study expands these prior studies by focusing on treatment initiation in OAC naïve incident AF patients, who had a clear recommendation for anticoagulant treatment.

Prior studies have found an increased risk of stroke in AF patients with schizophrenia *vs.* without schizophrenia,[3,4] which plausibly reflect the disparities in OAC treatment initiation. Nevertheless, the decision on OAC treatment initiation is a balance between stroke risk and bleeding risk.[5] Other studies have shown an increased risk of major bleeding and worse anticoagulation control when treated with warfarin in AF patients with schizophrenia *vs.* without.[3,7–9] Thus, the lower OAC initiation in patients with schizophrenia may reflect appropriate clinical concern about effectiveness and safety of anticoagulation in this clinically complex patient group. Further, the 1-year all-cause mortality was substantially higher in AF patients with schizophrenia than in patients without, and we cannot exclude that non-initiation to some extent may reflect appropriate considerations of risk versus benefit, and patient preferences in patients with an anticipated limited life expectancy. Recent studies have investigated broader physicatric conditions, such as "mental health conditions"[21] or bipolar/schizophrenic conditions.[22] Our results support these findings, and extends the current evidence to focus on AF patients who had a clear indication for stroke prevention treatment with OAC. Additionally, our results are underpinned by clinical endpoints, which highlights the importance of considering the competing risk of death when examining time-to-event outcomes in schizophrenic patients with prevalent AF. We did not adjust for socioeconomic status. Lunde et al. investigated the association of socioeconomic factors with treatment among a general AF population, and showed that such factors may partly explain the risk of initiating OAC treatment.[23] However, the observed association was strongly related to age and risk differences attenuated when including age in the adjustment models. Yet, our study must be interpreted in the context of residual confounding from lack of socioeconomic data.

Warfarin treatment has a narrow therapeutic window and is associated with numerous food and drug interactions. The introduction of NOACs has overcome some of the drawbacks of warfarin treatment, e.g. lower bleeding risk, in particular for intracranial haemorrhage and continuous dose adjustment with ongoing monitoring of the INR values.[5] In line with this, our results showed that OAC initiation improved among patients with schizophrenia following NOAC introduction, which reduced the gap between patients with and without schizophrenia; nevertheless, the difference remained substantial. From this study we cannot conclude whether this increase in OAC initiation was driven by NOACs or due to greater focus on disparities in cardiovascular treatment and outcome in this vulnerable patient population.[24] Nevertheless, most AF patients with schizophrenia were treated with NOACs (72.1%) during the period 2012–2018.

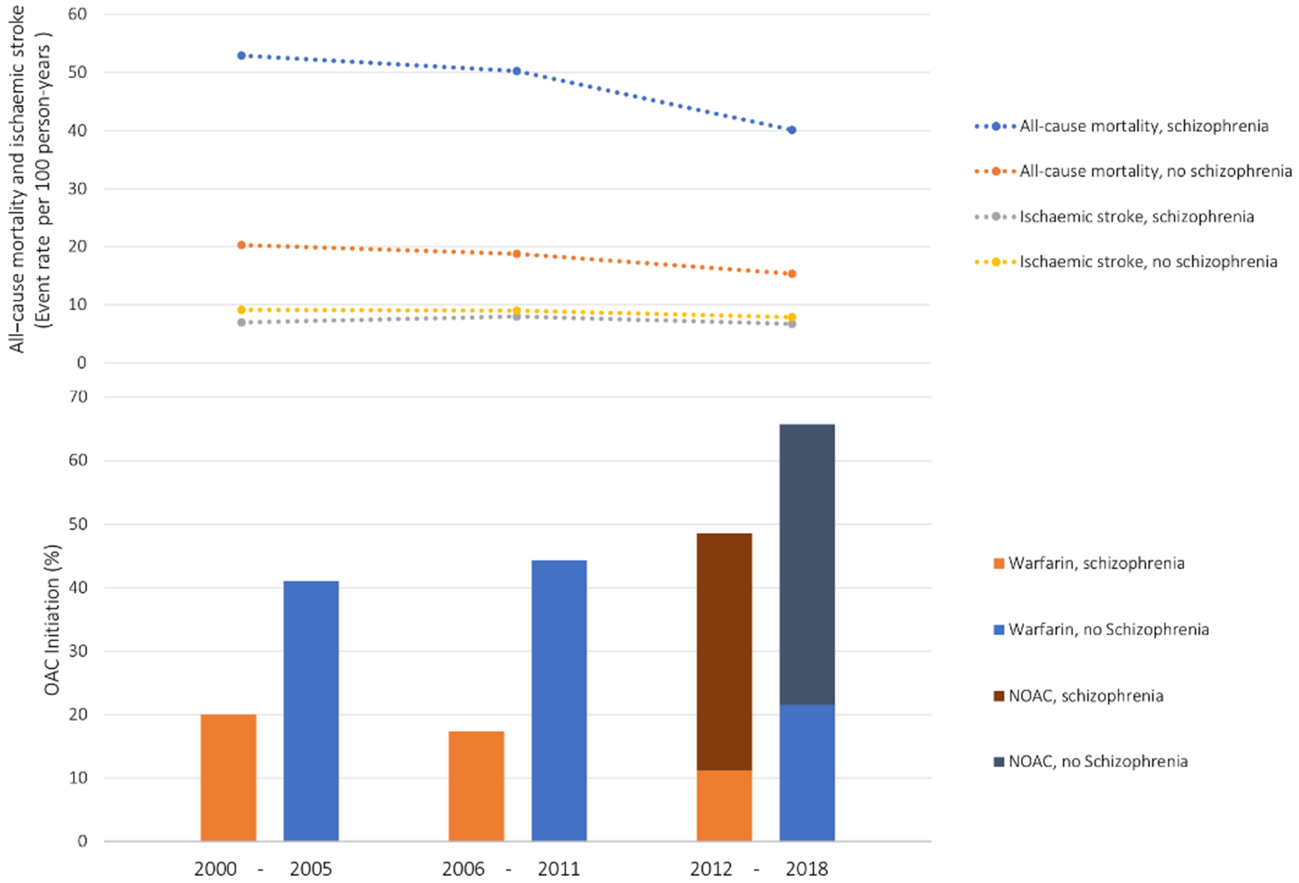

FIGURE 3 Temporal trends of OAC initiation and 1-year rates of ischaemic stroke and all-cause mortality according to schizophrenia status

4.1 | Strengths and limitations

The major strengths of this study are the large sample size and complete coverage in the Danish hospital discharge and prescription registries including all in- and outpatients with AF, which enabled complete follow-up for OAC initiation. Initiation of OAC was based on prescription claims. In Denmark, virtually all medical care is provided free of charge and costs of prescription medication after the first €131 is reimbursed up to 100%, with a maximum yearly co-payment of €548.[25] However, we cannot conclude whether lack of OAC initiation relates to patients not being prescribed OAC or not purchasing OAC prescriptions. Likewise, we have no information on whether the patients actually took their OAC drug.

Danish validation studies have previously found a positive predictive value of an AF diagnosis in the National Patient Register of 95%.[26] Assessment of schizophrenia was based on diagnoses in the hospital register, which may have led us to underestimate the prevalence.[27,28] However, we infer that in Denmark the majority of patients with schizophrenia are in contact with the hospital system due to the severity of this condition. Nevertheless, this could affect the generalizability of our findings, which may only pertain to patients with similar healthcare settings as in Denmark. We only had information on psychiatric admissions from 1995 onwards. Patients with a schizophrenia diagnosis before 1995 and no recorded diagnosis thereafter are therefore not included in the exposed cohort. We matched patients with schizophrenia to AF patients without according to perceived stroke risk at baseline. However, despite universal tax-supported health care in Denmark, cardiovascular diseases in patients with schizophrenia may have been underreported. For instance, we are not able to conclude whether the lower prevalence of hypertension in patients with schizophrenia reflect the true picture or underdiagnosis and undertreatment. Such potential misclassification may have affected our ability to adjust for differences in stroke risk. We also lacked data on behavioural risk factors such as alcohol, smoking and exercise, which could lead to residual confounding, e.g., bleeding risk due to alcohol abuse.[29] Nevertheless, we were able to adjust for hospital diagnosis of alcohol-related conditions. Similarly, our data did not allow us to ascertain the severity of the schizophrenic condition, such as syncopes or self-harming behaviour or other individual patient considerations that could affect physician willingness to prescribe OAC treatment.

5 | CONCLUSION

Initiation of OAC was substantially lower among patients with AF and schizophrenia compared with matched AF peers. These findings accentuate the importance of close attention to disparities in

initiation of OAC treatment, and potential missed opportunities for prevention of disabling strokes in AF patients with schizophrenia. Further studies are encouraged to explore potential reasons to remedy disparities in AF management in patients with schizophrenia.

COMPETING INTERESTS

Dr. Højen has received speaking fees from MSD and speaking and consulting fees from Bayer and Bristol-Myers Squibb/Phizer. Prof Larsen has served as an investigator for Janssen Scientific Affairs, LLC and Boehringer Ingelheim and received speaking and consulting fees from Bayer, Bristol-Myers Squibb/Pfizer, Boehringer Ingelheim, MSD and AstraZeneca. Dr. Nilsen has received speaking fees from Boehringer Ingelheim and BMS/Pfizer; consulting fees from Bayer and Daiichi-Sankyo; and grant support from BMS/Pfizer and Daiichi-Sankyo. Prof. Lip reports consultancy and speaker fees from BMS/Pfizer, Boehringer Ingelheim and Daiichi-Sankyo. Dr. Søgaard has received consulting fees from Bayer. The other authors declare no conflicts of interest.

CONTRIBUTORS

A.A.H., M.J. and M.S. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. A.A.H., M.S., P.B.N., S.R. and T.B.L. conceived and designed the study. A.A.H., M.S., M.J. and P.B.N. acquired, analysed or interpreted the data. A.A.H. drafted the manuscript, which was critically revised for important intellectual content by all of the authors. A.A.H., M.S., M.J. and P.B.N. conducted the statistical analysis. T.B.L. and M.J. provided administrative, technical or material support. The study was supervised by T.B.L. and G.Y.H.L.

DATA AVAILABILITY STATEMENT

Research data are not shared.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Højen AA, Nielsen PB, Riahi S, et al. Disparities in oral anticoagulation initiation in patients with schizophrenia and atrial fibrillation: A nationwide cohort study. *Br J Clin Pharmacol*. 2022;88(8):3847-3855. doi:10.1111/bcp.15337