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Atrial fibrillation in patients with severe mental disorders and the risk of stroke and fatal thromboembolic events: a nationwide cohort study

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ABSTRACT

Objectives: Outcomes of atrial fibrillation (AF) in patients with severe mental disorders are largely unknown. We therefore compared rates of stroke and fatal thromboembolic events in AF patients with and without mental disorders.

Design: Nationwide registry-based cohort study.

Setting: Denmark (population 5,6 million), 2000-2015.

Participants: AF patients with schizophrenia (n=534), severe depression (n=400), or bipolar disease (n=569) matched 1:5 on age, sex and calendar time to AF patients without mental disorders.

Exposure: Inpatient or hospital-based outpatient diagnosis of schizophrenia, severe depression or bipolar disease.

Primary and secondary outcome measures: Hazard ratios (HR) for stroke and fatal thromboembolic events comparing patients with and without mental disorders estimated by Cox regression with sequential adjustment for stroke risk factors, comorbidity, and oral anticoagulant therapy (OAT).

Results: Compared with matched comparisons, crude 5-year HRs of ischemic stroke was 1.20 (95% confidence intervals (CI) 0.76-1.87) for schizophrenia, 1.20 (95% CI 0.79-1.82) for depression, and 1.09 (95% CI 0.72-1.65) for bipolar disease. Equivalent HRs of hemorrhagic stroke were 1.16 (95% CI 0.79-1.70), 1.30 (95% CI 0.93-1.82), 1.18 (0.84-1.66), respectively. After adjusting for stroke risk factors, comorbidity, and initiation of oral anticoagulant (OAC) therapy these HR declined toward the null. Crude HRs of fatal thromboembolic events were 3.93 (95% CI 2.11-7.30) for schizophrenia, 0.82 (95% CI 0.43-1.56) for depression, and 1.54 (95% CI 0.92-2.56) for bipolar disease.

Conclusion: Severe mental disorders in AF patients were associated with increased risk of ischemic and in particular hemorrhagic stroke compared with matched comparisons. These excess stroke

rates were explained by higher prevalence of stroke risk factors, comorbidity and lower use of OAT. AF patients with schizophrenia also experienced higher mortality following thromboembolic events than matched comparisons.

Keywords: Atrial fibrillation, schizophrenia, depression, bipolar disease, stroke, outcome.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The study included all patients with a hospital diagnosis of atrial fibrillation in Denmark in 2000-2015. The study had complete follow-up on all participants from the nationwide Danish Civil Registration System.
- The study was conducted in a government financed healthcare system with equal access for the entire Danish population.
- Despite equal access to tax-supported health care in Denmark, diagnoses in patients with mental disorders may have been underreported.
- The study lacked data on alcohol, smoking, exercise, and other lifestyle related risk factors associated with increased risk of study outcomes. We were able to adjust for hospital diagnoses of alcohol-related conditions and other lifestyle-related diseases, but cannot exclude residual confounding.
- Finally, the data did not contain information on the quality and compliance with oral anticoagulant therapy.

INTRODUCTION

Cardiovascular diseases are highly prevalent in patients with severe mental disorders such as schizophrenia, bipolar disease and severe depression,[1] contributing to a 10-20 year shorter life expectancy than the general population.[2] Potential explanations include a high prevalence of cardiovascular risk factors such as smoking, dyslipidemia, hypertension, diabetes, and obesity.[3–5] In addition, antipsychotic medications may adversely affect cardiovascular disease risk via metabolic pathways involving dyslipidemia, weight gain, and diabetes.[6,7]

Atrial fibrillation (AF) is the most common cardiac arrhythmia, affecting up to 1-2% of the population in developed countries, and confers a substantial increased risk of stroke, heart failure and death.[8] Despite increasing clinical and research focus on cardiovascular diseases in AF patients with mental disorders, the stroke risk in patients with mental disorders is largely unknown. Prior studies have shown that AF patients with mental disorders are less likely to start oral anticoagulant therapy (OAT) than those without,[9,10] and that those who receive OAT have worse anticoagulation control[9,11,12] and increased risk of major haemorrhage.[11,13] However, these studies only assessed outcomes in patients receiving OAT for at least 100-180 days, excluding patients who never initiated therapy and those who discontinued therapy shortly after initiation.[11,13]

We aimed to examine the prognostic importance of severe mental disorders in AF patients. In a nationwide cohort of patients with incident AF, we conceived a matched cohort study to compare the risk of stroke and fatal thromboembolic events in AF patients with a prior diagnosis of schizophrenia, severe depression or bipolar disease to matched comparison cohorts without these disorders. By sequentially adjusting for stroke risk factors, comorbidity, and use of OAT, we sought to further characterize the association between mental disorders and AF outcomes.

METHODS

Data sources

This cohort study linked three well-established Danish nationwide; the National Patient Register[14], the National Prescription Register[15], and the Civil Registration System.[16] The National Patient Register holds information on dates of admission and discharge, and discharge diagnoses classified according to the *International Classification of Diseases* (ICD) for more than 99% of hospital admissions in Denmark. The Prescription Registry contains data on all prescription purchases by Danish residents since 1995. Data includes the patients' civil registration number, date of dispensing, and type and quantity of drug prescribed. The Danish Person Registry holds data on sex, date of birth, vital and emigration status. The appendix provides information on codes for diagnoses and medications. The registries were linked using the unique personal civil registration number assigned to all Danish residents, allowing a true population-based study covering all 5,6 million inhabitants of Denmark during the study period. We performed all linkages within Statistics Denmark, a governmental institution that collects and processes information for statistical and scientific purposes.[17] The study was approved by the Danish Data Protection Agency (Record number 2012-41-0633). According to Danish law, approval from an ethics committee is not required for anonymous registry-based studies.

Study population

We established a cohort of all patients with incident non-valvular AF, defining non-valvular AF as presence of AF, and baseline absence of mitral stenosis or mechanical heart valves. Specifically, we identified all patients discharged with a first hospital diagnosis of non-valvular AF between 2000 and 2015. We excluded patients who had not been residents in Denmark for at least 1 year before date of AF diagnosis (index date); patients with valvular AF; patients who died on the day of AF

diagnosis; and patients with a fatal thromboembolic event defined as death within the following 30 days of ischemic stroke, systemic embolism, pulmonary embolism or myocardial infarction before AF diagnosis. The positive predictive value (PPV) of an AF diagnosis in the National Patient Register is 95% (95% CI 89-98).[18]

Exposure

Through the National Patient Register, we identified all patients in the study population with an inpatient or outpatient diagnosis of schizophrenia, bipolar disease or severe depression before the index date. In Denmark, these mental disorders are primarily treated in public hospitals ensuring a high coverage of contacts with psychiatric disorders. The PPV of a diagnosis of mental disorders in the National Patient Register is 98% (95% CI 90-99).[18]

To control for confounding by reducing imbalance in the data and thereby model dependence and bias, we used Coarsened Exact Matching to produce a one-to-five match of patients with schizophrenia, severe depression, or bipolar disease on age, sex and calendar time (year of index date) to comparison cohorts of AF patients without mental disorders.[19] Patients age was grouped in approximately 5-year intervals based on the statistical software package Stata's (Stata Corp, version 14) function *cem*'s algorithm for automatic coarsening.[20] To evaluate the effect of matching on the balance between baseline variables we estimated the absolute standardized differences before and after matching.

Patient characteristics

Baseline comorbidity was defined according to medication claims within the year before the AF diagnosis and/or history of primary or secondary hospital discharge diagnoses (excluding

emergency room diagnoses) since 1994. Comorbidity information included cardiovascular and metabolic diseases, and lifestyle related diseases (e.g., alcohol-related diseases such as alcoholic liver disease, and alcoholic polyneuropathy, cardiomyopathy, gastritis or myopathy, and alcohol-induced pancreatitis). We further combined baseline information into the CHA_2DS_2VASc stroke risk score[21] to summarize perceived stroke risk at baseline, and the HAS-BLED score[22] as a measure of bleeding risk at baseline (see score definitions in Supplementary Table 2).

Outcomes

Study outcomes were ischemic stroke, hemorrhagic stroke (intracranial bleeding), and fatal thromboembolic events. We derived all outcomes from hospital diagnoses in the National Patient Register. Stroke diagnoses were required to be primary in-hospital codes, excluding emergency room and ambulatory diagnoses, to ensure higher validity.

Statistical analyses

We followed all patients from their AF diagnosis and up to five years after baseline. Follow-up was censored at time of death, migration, study end (November 21, 2016), or the outcome of interest, whichever came first. Patient baseline characteristics were presented as proportions for discrete variables and means with standard deviations (SD) for continuous variables. Crude incidence rates were calculated as number of events divided by person-time. Cumulative incidence functions (by means of the Aalen-Johansen estimator), assuming death as competing risk, were used to depict risk of outcome during follow-up. We assessed the association between each mental disorder and study outcome using Cox Proportional hazard regression with stratification on the matched groups. To assess to which extend the observed association could be explained by comorbidity and/or use of OAT, we performed sequential cumulative adjustment for 1) stroke risk as summarized by

components of the CHA_2DS_2VASc and HAS-BLED scores, and comorbidities not included in CHA_2DS_2VASc and HAS-BLED (chronic pulmonary disease, cancer, and venous thromboembolism), and 2) use of OAT during follow-up modelled as a time-varying covariate shifting from untreated to treated status at first observed prescription of any OAC. We excluded age and sex in the CHA_2DS_2VASc and HAS-BLED scores as these were included as matching factors and perfectly balanced between comparison cohorts (Supplementary Table 3). The distribution of time to OAC treatment initiation was presented by cumulative incidence curves (Supplementary Figure 2). Point estimates were reported with 95% confidence intervals (CI) and a p-value less than 0.05 was considered statistically significant.

RESULTS

We identified 260,974 AF patients during the study period. After exclusions, the study cohort comprised 253,741 AF patients of which 534 patients had schizophrenia, 400 severe depression, and 569 bipolar disease (Supplementary Figure 1). Table 1 shows baseline characteristics according to presence and type of mental disorder. AF patients with schizophrenia were substantially younger (mean age 64.5 years) whereas the age of patients with severe depression (73.7 years) and bipolar disease (73.0 years) was comparable with patients without mental disorders (73.3 years). Baseline stroke risk appeared lower in patients with schizophrenia; mean CHA_2DS_2-VASc score was 2.4 versus 3.0 in patients without mental disorders. However, this was explained by the lower age of schizophrenic patients. After matching, the mean CHA_2DS_2-VASc score was 2.3 in AF patients without schizophrenia (Supplementary Table 3). The CHA_2DS_2-VASc score was 3.5 in patients with severe depression and 3.2 in patients with bipolar disease (Table 1). The higher CHA_2DS_2-VASc score in patients with severe depression was primarily driven by a large proportion with prior stroke (30.3% vs. 16.9% in comparisons). In comparison 14.2% of schizophrenic patients had prior stroke; they also had lower prevalence of hypertension, myocardial infarction, and peripheral arterial disease. Compared with patients with no mental disorder, the HAS-BLED score was also higher in patients with severe depression and bipolar disease whereas it was lower in patients with schizophrenia. Alcohol-related diseases were prevalent across all mental disorders, particularly for patients with schizophrenia or bipolar disease (~20% vs. 4% in comparisons). Supplemental Table 3 shows characteristics for patients with schizophrenia, severe depression, and bipolar disease and their matched comparisons.

Ischemic stroke

Figure 1 displays cumulative incidence curves for ischemic stroke in the matched cohorts. Rates of ischemic stroke at 5 years was 1.96 events per 100 person-years in schizophrenic AF patients vs.

1.37 in matched comparisons, yielding a crude HR of 1.20 (95% CI 0.76-1.87) with confidence intervals including unity (Table 2). After adjustment for stroke risk as summarized by the CHA_2DS_2-VASc and HAS-BLED scores and other comorbidities this HR was 0.98 (95% CI 0.61-1.58) (Figure 2). Rates of OAT initiation in AF patients with mental disorders was substantially lower than in matched comparisons (Supplementary Figure 2), and after additional adjustment for OAT use during follow-up the HR of ischemic stroke was 0.91 (95% CI 0.56-1.46) (Figure 2). Similarly, the crude HR of 1.20 (95% CI 0.79-1.82) at 5-years in patients with severe depression was substantially attenuated by sequential adjustment for stroke risk factors, comorbidity, and OAT (HR 0.93, 95% CI 0.60-1.43) (Figure 2). This pattern of diminishing HRs with sequential adjustment for stroke risk factors and OAT was less evident in patients with bipolar disease in whom the crude HR was 1.09 (95% CI 0.72-1.65) and the fully adjusted HR was 0.92 (95% CI 0.60-1.42). Thus, compared with AF patients without mental disorders, the fully adjusted HRs of ischemic stroke were comparable across all mental disorders with wide CIs that crossed unity (Figure 2).

Hemorrhagic stroke

The cumulative incidence curves showed higher rates of hemorrhagic stroke in patients with mental disorders than in their matched comparisons, in particular for patients with severe depression and bipolar disease (Figure 3). At 5 years, the rate of hemorrhagic stroke was 2.61 events per 100 person-years in schizophrenic patients vs. 2.01 in matched comparisons (crude HR of 1.16, 95% CI 0.79-1.70), 4.68 per 100 person-years in patients with severe depression vs. 3.28 in matched comparisons (crude HR of 1.30, 95% CI 0.93-1.82), and 3.03 vs. 2.38 in patients with bipolar disease (HR of 1.18, 95% CI 0.84-1.66) (Table 2, Figure 2). Sequential adjustment for stroke risk factors, comorbidity, and OAT use attenuated this association and the fully adjusted HRs of

hemorrhagic stroke were comparable with matched comparisons across all mental disorders with wide CIs including unity (Figure 2).

Fatal thromboembolic events

During 5-years follow-up, 19 fatal thromboembolic events occurred in AF patients with schizophrenia, 20 in patients with bipolar disease, and 11 in patients with severe depression. Accordingly, rates of fatal thromboembolic events per 100 person-years was substantially lower than rates of ischemic and hemorrhagic stroke; 1.43 for schizophrenia vs. 0.36 in matched comparisons, 1.03 vs. 1.15 for severe depression, and 1.41 vs. 0.88 for patients with bipolar disease (Table 2). Notwithstanding, due to the low rate in the matched comparisons, cumulative incidence curves revealed distinct differences in rates of fatal thromboembolic events in patients with schizophrenia vs. matched comparisons (Figure 4). The equivalent 5-year HR was 3.93 (95% CI 2.11-7.30) decreasing to 3.37 (95% CI 1.77-6.43) after adjustment for stroke risk factors, comorbidity, and OAT (Figure 2). Cumulative incidence curves in patients with severe depression vs. matched comparisons overlapped (crude HR of 0.82, 95% CI 0.42-1.56). After adjustment for stroke risk factors, comorbidity, and OAT, the HR was 0.55 (95% CI 0.28-1.07). In patients with bipolar disease the crude HR was 1.54 (95% CI 0.92-2.56) compared with matched comparisons. Sequential adjustment gradually attenuated this association (HR of 1.17, 95% CI 0.69-2.00) (Figure 2).

DISCUSSION

Principal findings

This nationwide cohort study revealed a low prevalence of severe mental disorders among patients with incident AF in Denmark. Patients with mental disorders experience higher risk of stroke compared with matched AF patients without mental disorders, although the differences were not statistically significant. However, after sequential adjustment for stroke risk factors, comorbidity and use of OAT, stroke rates were comparable with matched comparisons, suggesting that the excess stroke risk in patients with mental disorders stem from higher prevalence of stroke risk factors and lower receipt of OAT. Few thromboembolic events occurred during follow-up. Nonetheless, we noted a substantially higher mortality after a thromboembolic event in patients with schizophrenia than in matched comparisons.

Strengths and limitations

These estimates of stroke risk and thromboembolic events in AF patients are based on a nationwide cohort study conducted in a setting where virtually all medical care is provided free of charge, and with complete follow-up through nationwide registries. Nonetheless, despite universal tax-supported health care in Denmark, diagnoses in patients with mental disorders may have been underreported.[23,24] From the current study, we are not able to conclude whether the low prevalence of AF patients with mental disorders reflect the true picture or whether AF may be under-diagnosed in these patients. We included only patients with mental disorders recorded in the hospital register, and the prevalence is likely underestimated, mainly with regard to severe depression. However, we infer that the majority of patients with schizophrenia and bipolar disease are in contact with the psychiatric hospital system due the severity of these conditions. It is also important to note that we only had information on psychiatric admissions from 1995 onwards. Thus, patients with a diagnosis before 1995 and no recorded diagnosis thereafter would not be included in the exposed cohort. Lack

of data on alcohol, smoking, exercise, and other lifestyle related risk factors associated with increased risk of study outcomes is another limitation. We were able to adjust for hospital diagnoses of alcohol-related conditions and many other lifestyle-related diseases including chronic pulmonary disease, diabetes, liver disease, cardiovascular disease, and cancer, which were more prevalent among patients with mental disorders. Nonetheless, incomplete control for these factors likely lead to residual confounding, e.g. bleeding risk due to alcohol abuse.[25,26] Finally, our data did not contain information on the quality and compliance with OAT, which may be lower among patients with mental disorders due to cognitive limitations and maladaptive behaviours.[27]

Comparison with other studies

Our findings are concordant with two prior studies on outcomes of AF patients with mental disorders receiving warfarin.[11,13] In a US cohort study of 9,345 Medicaid recipients receiving two or more warfarin prescriptions less than 100 days apart, Schauer et al[13] demonstrated HRs of 1.36 (95% CI 1.06-1.74) for ischemic stroke and 1.46 (95% CI 1.04-2.05) for hemorrhagic stroke in patients with mental disorders illnesses compared with patients without. In another US cohort study, Paradise et al[11] showed that mental disorders was associated with an increased risk of major bleeding (HR:1.19, 95% CI 1.11-1.27) in patients with any mental disorder vs. propensity matched comparisons in 103,897 patients receiving warfarin for at least 6 months through the Veterans Health Administration. Both studies only included patients who were considered appropriate for OAT and who actually received it and remained successfully on treatment for an extended period. Thus, these results may not reflect stroke risk in all patients with mental disorders.

Our findings expand prior studies by including all AF patients regardless of OAT use. We saw a noticeable lower rate of OAT initiation in patients with mental disorders compared with matched

comparisons, which is in line with prior studies showing that AF patient with mental disorders are less likely to receive OAT.[9,10] Schmitt et al[10] found that AF patients with mental disorders had higher prevalence of stroke risk factors and contraindications to OAT. Thus, lower treatment rates in patients with mental disorders may reflect appropriate attention to bleeding risk. On the other hand, when restricting to patients eligible for OAT, patients with mental disorders remained less likely to receive OAT.[10] As the higher stroke rates in our study appeared to be due to differences in stroke risk factors, comorbidity, and receipt of OAT, any disparities in the care of AF patients with mental disorders requires close attention. Other studies have shown that patients with mental disorders have worse OAT control.[9,11,12] Walker et al[9] found that when prescribed warfarin, AF patients with mental disorders were substantially more likely to have highly supra-therapeutic International Normalized Ratio (INR) values than those without mental disorders (27.3% vs. 1.6% had at least one INR measurement above 5.0). However, this assessment was based on a sub-cohort of only 84 AF patients and should be interpreted with caution.

The higher mortality within the 30-days following a thromboembolic event in patients with schizophrenia is of concern and emphasizes the need for vigilant follow-up in this patient population. The finding is in line with prior studies reporting increased cardiac mortality in patients with schizophrenia.[24,28] Future studies are encouraged to explore potential reasons which are likely multifactorial and may entail both severity of illness, comorbidity, quality of care, and factors beyond patient care.[29]

Conclusions

In conclusion, this study showed that mental disorders in patients with AF is associated with increased risk of ischemic and hemorrhagic stroke. When sequentially controlling for stroke risk

factors, comorbidity, and OAT use the hazard rates attenuated and were comparable with matched comparisons, indicating that the excess stroke risk is due to a higher prevalence of stroke risk factors and lower use of OAT in patients with mental disorders. Patients with schizophrenia also experienced higher mortality following a thromboembolic event than matched comparisons. These findings highlight the importance of close attention to stroke risk factors and potential disparities in receipt of OAT in AF patients with mental disorders. Our findings also identify challenges in the management of AF patients with mental disorders; the excess burden of stroke risk factors signifies the need for stroke prevention whereas the high rates of hemorrhagic stroke emphasize that that cautious assessment of bleeding may be particularly pertinent for patients with mental disorders, indicating a need for optimized coordination between specialist physical and mental health service.

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Author Contributions

MS, FS and JNK had full access to all of the data in this study and take responsibility for the integrity of the data and the accuracy of the data analysis. SR, SPJ and TBL provided the idea for the study. MS, FS, TBL and SR defined the study concept and performed the critical interpretation of the data. MS drafted the article. All authors contributed critical revisions and approved the final version to be published.

Conflicts of Interest Disclosures

Associate Professor Larsen has served as an investigator for Janssen Scientific Affairs, LLC and Boehringer Ingelheim and has served as a speaker for Bayer, BMS/Pfizer, Boehringer Ingelheim. Senior Statistician Flemming Skjøth has served as a consultant for Bayer. Other authors – none declared.

Role of the Funders/Sponsors

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Ethics approval: The study was approved by the Danish Data Protection Agency (Record number 2012-41-0633).

Data sharing statement: No additional data are available

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FIGURE LEGENDS

Figure 1. Cumulative incidence of ischemic stroke in patients with atrial fibrillation and mental disorders and matched atrial fibrillation patients without mental disorders.

Figure 2. Crude and adjusted hazard ratios (HR) with 95% confidence intervals (CI) for ischemic stroke, hemorrhagic stroke, and fatal thromboembolic events in atrial fibrillation patients with severe mental disorders compared with matched atrial fibrillation patients without mental disorders.

Figure 3. Cumulative incidence of hemorrhagic stroke in patients with atrial fibrillation and mental disorders and matched atrial fibrillation patients without mental disorder.

Figure 4. Cumulative incidence of fatal thromboembolic events in patients with atrial fibrillation and mental disorders and matched atrial fibrillation patients without mental disorder.

Table 1. Descriptive characteristics of patients with incident atrial fibrillation in Denmark according to presence of mental health disorders.

Characteristic, % (N)	No mental disorder (N=252,238)	Schizophrenia (N=534)	Severe depression (N=400)	Bipolar disease (N=569)
Demographic characteristics				
Females	46.7 (117,876)	45.7 (244)	61.8 (247)	59.6 (339)
Mean age (SD)	73.3 (13.1)	64.5 (13.7)	73.7 (14.0)	73.0 (11.2)
Stroke risk factors and comorbidity				
Mean CHA_2DS_2VASc score (SD)	3.0 (1.8)	2.4 (1.7)	3.5 (1.9)	3.2 (1.7)
Mean HASBLED score (SD)	2.3 (1.3)	2.0 (1.4)	2.7 (1.5)	2.6 (1.4)
Prior stroke	16.9 (42,585)	14.2 (76)	30.3 (121)	20.2 (115)
Heart failure	17.0 (42,910)	23.4 (125)	20.3 (81)	21.1 (120)
Hypertension	42.6 (107,332)	26.6 (142)	44.5 (178)	36.6 (208)
Myocardial infarction	10.3 (26,089)	8.2 (44)	11.3 (45)	9.3 (53)
Peripheral arterial disease	7.6 (19,266)	6.7 (36)	10.0 (40)	9.0 (51)
Diabetes	12.9 (32,606)	24.3 (130)	15.8 (63)	20.2 (115)
Prior bleeding	26.4 (66,694)	28.1 (150)	44.0 (176)	37.6 (214)
Renal dysfunction	5.2 (13,003)	10.1 (54)	8.5 (34)	15.8 (90)
Prior venous thromboembolism	4.8 (12,081)	7.3 (39)	10.8 (43)	10.0 (57)
Chronic pulmonary disease	14.5 (36,615)	28.7 (153)	22.3 (89)	30.8 (175)
Cancer	15.9 (40,171)	12.9 (69)	14.8 (59)	17.0 (97)
Alcohol-related disease	4.2 (10,471)	19.1 (102)	11.0 (44)	20.9 (119)
Medication use within 365 days before index date				
Coumarin	14.4 (36,326)	5.1 (27)	8.8 (35)	12.1 (69)
NOAC	2.5 (6,347)	3.4 (18)	2.3 (9)	2.3 (13)
Aspirin	37.6 (94,951)	33.0 (176)	40.5 (162)	38.1 (217)
Clopidogrel	4.3 (10,936)	5.6 (30)	9.0 (36)	5.6 (32)
NSAID	26.7 (67,468)	25.1 (134)	27.3 (109)	25.0 (142)

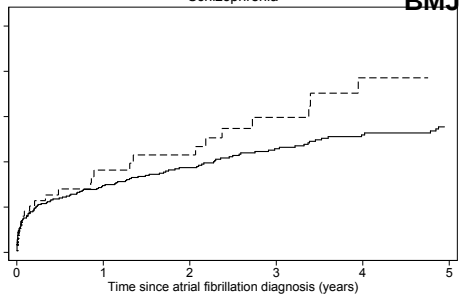
Digoxin	12.4 (31,200)	9.9 (53)	8.8 (35)	12.1 (69)
Non-loop diuretics	36.2 (91,336)	25.1 (134)	38.8 (155)	34.4 (196)
Loop-diuretics	25.5 (64,337)	34.8 (186)	28.8 (115)	36.0 (205)
Beta-blocker	32.2 (81,335)	22.7 (121)	28.0 (112)	24.3 (138)
Calcium channel blocker	25.5 (64,355)	17.0 (91)	31.0 (124)	25.1 (143)
Renin-angiotensin inhibitor	35.5 (89,621)	23.8 (127)	37.5 (150)	32.0 (182)
Statins	24.6 (62,166)	23.2 (124)	26.0 (104)	27.4 (156)

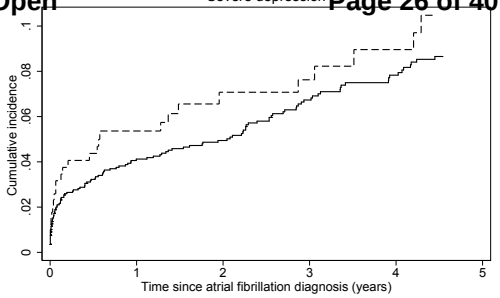
Abbreviations:
SD: Standard deviation
NOAC: Non-vitamin K oral anticoagulant
NSAID: Non-steroidal anti-inflammatory drugs

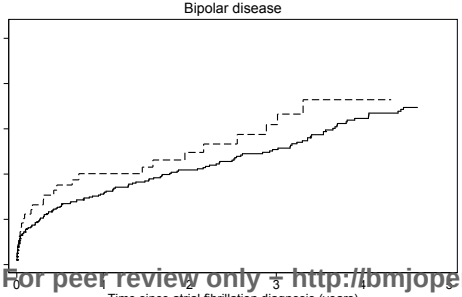
Table 2. Number of events and rates of stroke and fatal thromboembolic events at 5 years following incident atrial fibrillation.

Characteristic	Patients	Ischemic stroke		Hemorrhagic stroke		Fatal thromboembolic events	
	N	Events, N	Rate	Events, N	Rate	Events, N	Rate
Entire unmatched AF comparison cohort	252,238	15,710	2.03	21,563	2.83	8,039	1.00
Schizophrenia							
Schizophrenia	534	25	1.96	33	2.61	19	1.43
Matched comparison cohort	2,669	120	1.37	174	2.01	33	0.36
Severe depression							
Severe depression	400	28	2.74	46	4.68	11	1.03
Matched comparison cohort	2,000	128	2.15	191	3.28	71	1.15
Bipolar disease							
Bipolar disease	569	28	1.68	41	3.03	20	1.41
Matched comparison cohort	2,845	147	2.04	205	2.38	79	0.88

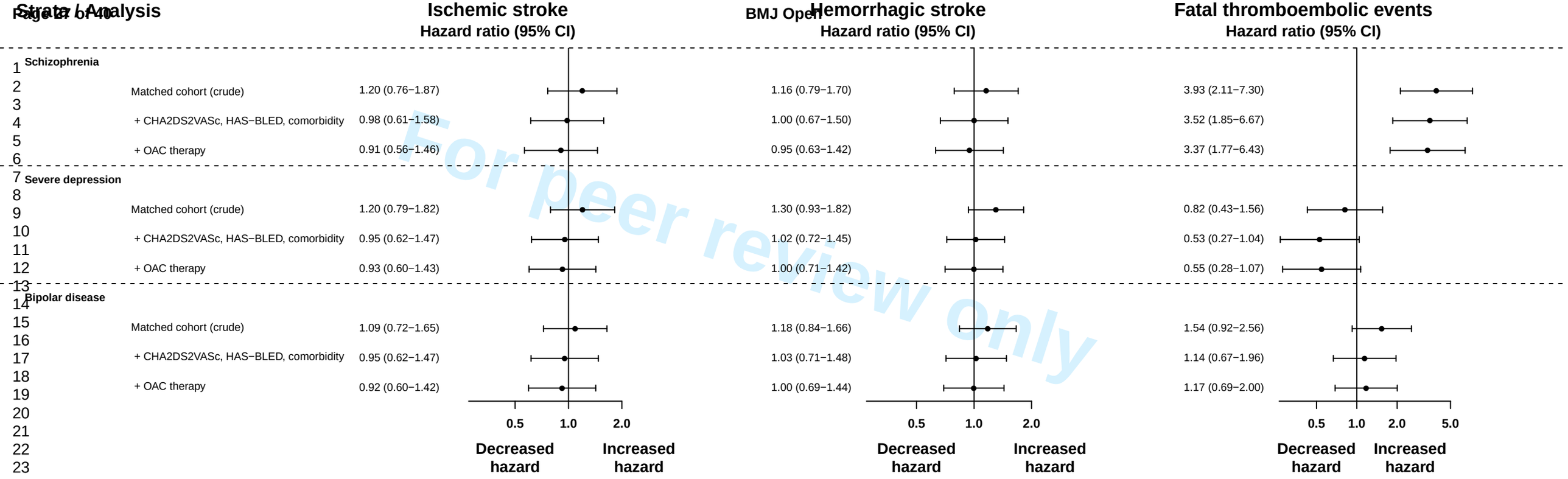
Rates are calculated as number of events divided by person-time per 100 years.

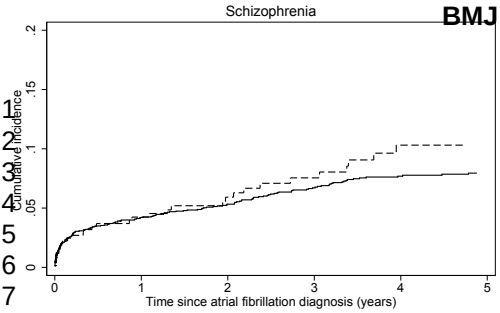


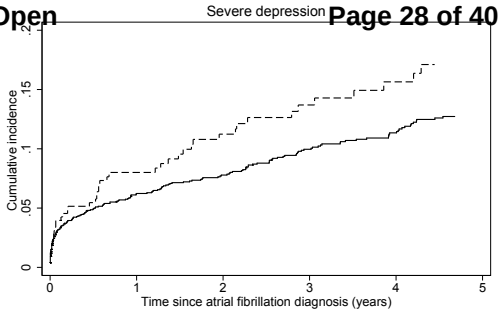


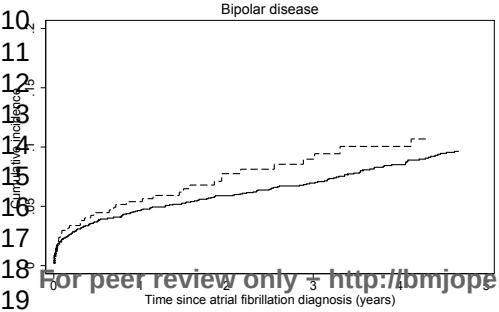


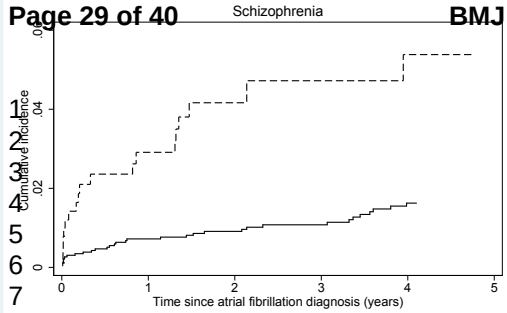
Strata Analysis

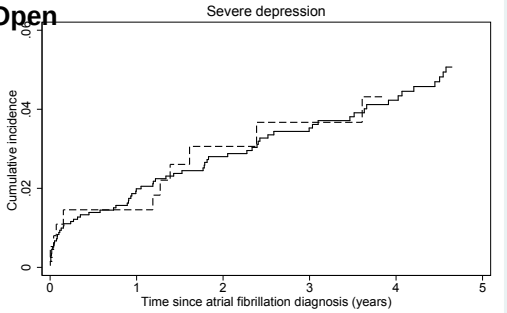


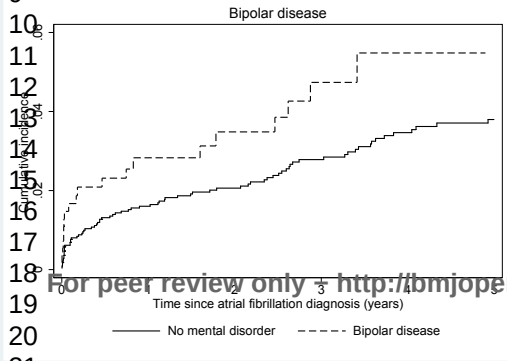












SUPPLEMENTAL INFORMATION

Atrial fibrillation in patients with severe mental disorders and the risk of stroke and fatal thromboembolic events: a nationwide cohort study

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Supplementary tables and figures

Supplementary Table 1: Definitions on comorbidity and concomitant medication according to ICD-10 codes and ATC-codes.

Supplementary Table 2: Risk score definitions

Supplementary Table 3: Descriptive characteristics of AF patients with schizophrenia, severe depression, or bipolar disease and their matched comparison cohorts.

Supplementary Figure 1: Flowchart of the study population.

Supplementary Figure 2: Cumulative incidence curves of initiation of oral anticoagulation therapy in age, sex and calendar time matched atrial fibrillation patients with and without mental disorders.

Supplementary Table 1. Definitions on comorbidity and concomitant medication according to ICD-10 codes and ATC-codes.

Diagnoses	International Classification of Diseases 10th revision (ICD-10) code	Anatomical Therapeutic Chemical (ATC) code
Schizophrenia	F20	
Bipolar disease	F30 F31	
Severe depression	F322 F323 F332 F333	
Atrial fibrillation	I48	
Ischemic stroke	I63 I64	
Systemic embolism	I74	
Pulmonary embolism	I26	
Myocardial infarction	I21 I23	
Heart failure	I110 I130 I132 I420 I50	
Hypertension		See specified definition[a]
Peripheral vascular/ischemic disease	I702 I703 I704 I705 I706 I707 I708 I709 I71 I739	
Diabetes	E100 E101 E109 E110 E111 E119	A10
Prior bleeding	K250 K252 K254 K260 K262 K264 K270 K272 K274 K280 K282 K290 K920 K921 K922 D62 J942 H113 H356 H431 N02 R04 R31 R58	
Renal dysfunction	I12 I13 N00 N01 N02 N03 N04 N05 N07 N11 N14 N17 N18 N19 Q61	
Prior VTE	I801 I802 I803 I808 I809 I819 I636 I676 I822 I823 I828 I829	
Chronic pulmonary disease	J40 J41 J42 J43 J44 J45 J46 J47 J60 J61 J62 J63 J64 J65 J67 J684 J701 J703 J841 J920 J961 J982 J983	
Cancer	C	
Alcohol-related disease	E224 E529A F10 G312 G621 G721 I426 K292 K70 K860 L278A O354 T51 Z714 Z721	

Medications within 365 days before index date		
Coumarin		B01AA
NOAC		B01AF01 B01AF02 B01AE07
Aspirin		B01AC06
Clopidogrel		B01AC04
NSAID		M01A
Digoxin		C01AA05
Non-loop diuretics		C02DA C02L C03A C03B C03D C03E C03X C07C C07D C08G C09BA C09DA C09XA52
Loop-diuretics		C03C
Beta-blocker		C07
Calcium channel blocker		C07F C08 C09BB C09DB
Renin-angiotensin inhibitor		C09
Statins		C10

Abbreviations: VTE, venous thromboembolism; NOAC, Non-vitamin K oral anticoagulant; NSAID, Non-steroidal anti-inflammatory drugs.

[a]We identified subjects with hypertension from combination treatment with at least two of the following classes of antihypertensive drugs:

I· Alpha adrenergic blockers (C02A, C02B, C02C)

II· Non-loop diuretics (C02DA, C02L, C03A, C03B, C03D, C03E, C03X, C07C, C07D, C08G, C09BA, C09DA, C09XA52)

III· Vasodilators (C02DB, C02DD, C02DG, C04, C05)

IV· Beta blockers (C07)

V· Calcium channel blockers (C07F, C08, C09BB, C09DB)

VI· Renin-angiotensin system inhibitors (C09)

Supplementary Table 2. Risk score definitions.

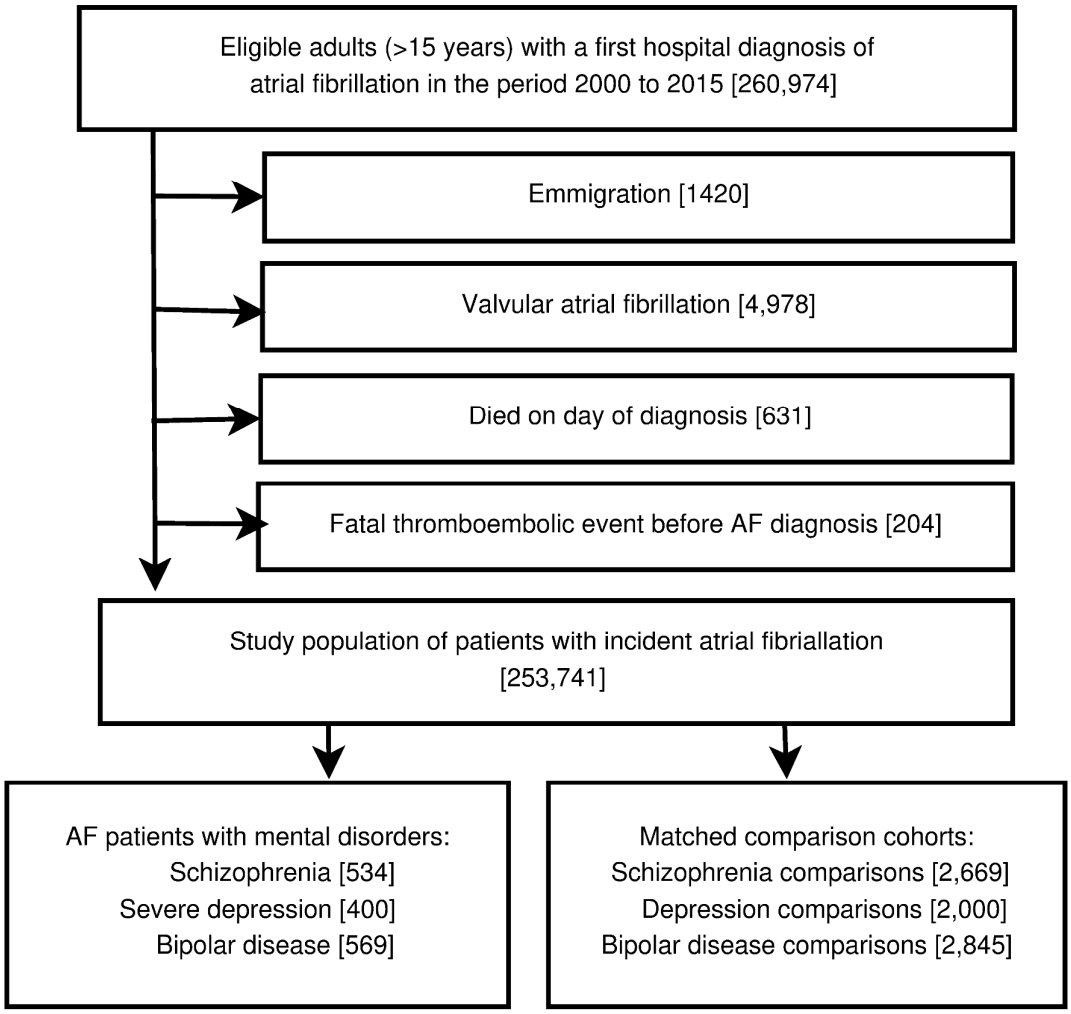
Risk score	Points if present
CHA_2DS_2VASc[a]	
Congestive heart failure or Left Ventricular Dysfunction	1
Hypertension	1
Age ≥ 65 years	1
Age ≥ 75 years	1
Diabetes mellitus	1
Stroke (ischemic stroke, transient ischemic disease or systemic embolism)	2
Vascular disease (myocardial infarction, peripheral arterial disease, or aortic plaque)	1
Sex category (female)	1
HAS-BLED[b]	
Hypertension	1
Abnormal renal function	1
Abnormal hepatic function	1
Stroke (ischemic stroke or transient ischemic attack)	1
Bleeding	1
Labile international normalized ratio[c]	1
Elderly age (≥ 65 years)	1
Drugs (aspirin, clopidogrel, or non-steroidal anti-inflammatory drugs)	1
Alcohol intake	1

[a]Reflects stroke risk in atrial fibrillation patients not in anticoagulant therapy (Lip GYH, Nieuwlaat R, Pisters R, Lane DA, Crijns HJGM. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. Chest 2010;137(2):263-72)

[b]Reflects bleeding risk in atrial fibrillation patients undergoing anticoagulant therapy (Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJGM, Lip GYH. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. Chest 2010;138(5):1093-100).

[c]Not included due to unavailable information

Supplementary Figure 1. Flowchart of the study population.



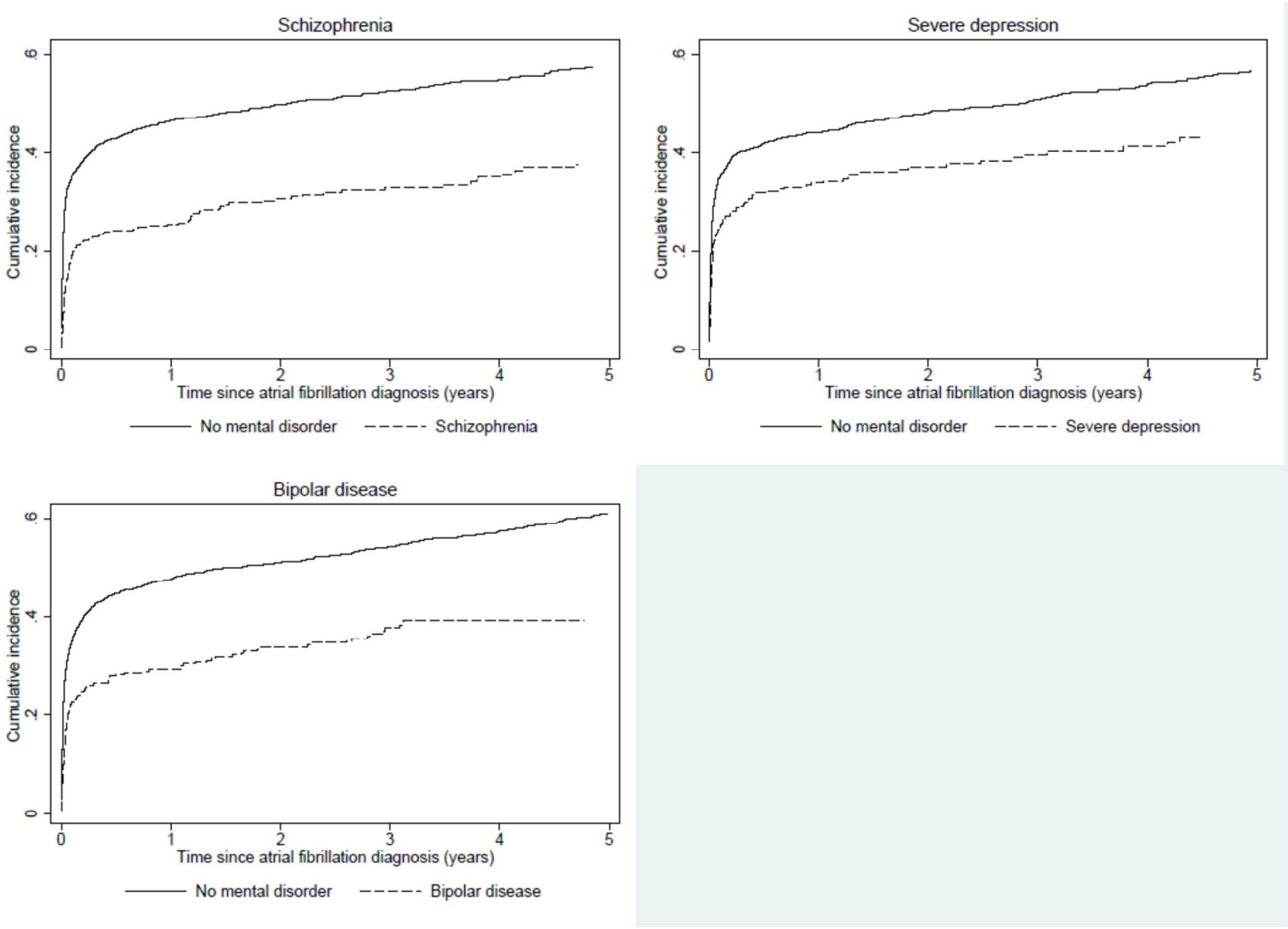
Supplementary Table 3. Descriptive characteristics of AF patients with schizophrenia, severe depression, or bipolar disease and their matched comparison cohorts.

Characteristic, % (N)	Schizophrenia		Severe depression		Bipolar disease	
	Matched AF comparisons	Schizophrenia	Matched AF comparisons	Severe depression	Matched AF comparisons	Bipolar disease
Total number	2,669	534	2,000	400	2,845	569
Females	45.7 (1,219)	45.7 (244)	61.8 (1,235)	61.8 (247)	59.6 (1,695)	59.6 (339)
Mean age (SD)	64.6 (13.8)	64.5 (13.7)	73.5 (14.0)	73.7 (14.0)	73.0 (11.2)	73.0 (11.2)
Mean CHA_2DS_2VASc score (SD)	2.3 (1.8)	2.4 (1.7)	3.2 (1.8)	3.5 (1.9)	3.1 (1.7)	3.2 (1.7)
Mean HASBLED score (SD)	1.9 (1.4)	2.0 (1.4)	2.3 (1.4)	2.7 (1.5)	2.3 (1.3)	2.6 (1.4)
Prior stroke	13.5 (361)	14.2 (76)	17.4 (347)	30.3 (121)	15.4 (439)	20.2 (115)
Heart failure	14.1 (375)	23.4 (125)	16.8 (335)	20.3 (81)	15.8 (449)	21.1 (120)
Hypertension	39.6 (1,057)	26.6 (142)	42.5 (850)	44.5 (178)	46.9 (1,334)	36.6 (208)
Myocardial infarction	8.9 (237)	8.2 (44)	10.3 (206)	11.3 (45)	9.9 (282)	9.3 (53)
Peripheral arterial disease	6.4 (171)	6.7 (36)	8.4 (168)	10.0 (40)	7.7 (218)	9.0 (51)
Diabetes	12.8 (342)	24.3 (130)	13.1 (261)	15.8 (63)	13.5 (384)	20.2 (115)
Prior bleeding	21.0 (560)	28.1 (150)	27.1 (543)	44.0 (176)	25.0 (710)	37.6 (214)
Renal dysfunction	4.5 (119)	10.1 (54)	5.4 (108)	8.5 (34)	4.7 (133)	15.8 (90)
Prior venous thromboembolism	4.6 (124)	7.3 (39)	4.6 (92)	10.8 (43)	5.8 (165)	10.0 (57)
Chronic pulmonary disease	12.9 (343)	28.7 (153)	15.6 (311)	22.3 (89)	15.6 (444)	30.8 (175)
Cancer	12.5 (334)	12.9 (69)	17.8 (355)	14.8 (59)	16.8 (477)	17.0 (97)
Alcohol-related disease	5.2 (138)	19.1 (102)	3.8 (75)	11.0 (44)	3.9 (112)	20.9 (119)

Coumarin	14.8 (394)	5.1 (27)	13.1 (262)	8.8 (35)	14.2 (403)	12.1 (69)
NOAC	3.0 (81)	3.4 (18)	3.0 (60)	2.3 (9)	3.7 (106)	2.3 (13)
Aspirin	29.6 (791)	33.0 (176)	39.2 (784)	40.5 (162)	35.9 (1021)	38.1 (217)
Clopidogrel	4.5 (121)	5.6 (30)	5.5 (110)	9.0 (36)	5.2 (147)	5.6 (32)
NSAID	26.5 (707)	25.1 (134)	26.4 (529)	27.3 (109)	27.3 (776)	25.0 (142)
Digoxin	8.2 (220)	9.9 (53)	10.2 (204)	8.8 (35)	10.5 (298)	12.1 (69)
Non-loop diuretics	30.3 (808)	25.1 (134)	36.9 (737)	38.8 (155)	38.9 (1107)	34.4 (196)
Loop-diuretics	18.0 (480)	34.8 (186)	24.7 (494)	28.8 (115)	25.0 (711)	36.0 (205)
Beta-blocker	32.6 (870)	22.7 (121)	33.1 (662)	28.0 (112)	36.0 (1023)	24.3 (138)
Calcium channel blocker	23.4 (625)	17.0 (91)	25.2 (504)	31.0 (124)	26.0 (741)	25.1 (143)
Renin-angiotensin inhibitor	34.8 (929)	23.8 (127)	37.6 (753)	37.5 (150)	39.5 (1125)	32.0 (182)
Statins	27.0 (721)	23.2 (124)	28.6 (573)	26.0 (104)	27.8 (790)	27.4 (156)

Abbreviations:
SD: Standard deviation
NOAC: Non-vitamin K oral anticoagulant
NSAID: Non-steroidal anti-inflammatory drugs

Supplementary Figure 2. Cumulative incidence curves of initiation of oral anticoagulation therapy in age, sex and calendar time matched atrial fibrillation patients with and without mental disorders.



STROBE (Strengthening The Reporting of OBservational Studies in Epidemiology) Checklist

A checklist of items that should be included in reports of observational studies. You must report the page number in your manuscript where you consider each of the items listed in this checklist. If you have not included this information, either revise your manuscript accordingly before submitting or note N/A.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Section and Item	Item No.	Recommendation	Reported on Page No.
Title and Abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/Rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study Design	4	Present key elements of study design early in the paper	1, 2, 5, 6-9
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-9
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6
		Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	N/A
		Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants	N/A
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed	7
		Case-control study—For matched studies, give matching criteria and the number of controls per case	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-9

Section and Item	Item No.	Recommendation	Reported on Page No.
Data Sources/ Measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-9
Bias	9	Describe any efforts to address potential sources of bias	7-9
Study Size	10	Explain how the study size was arrived at	6-7
Quantitative Variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-9
Statistical Methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8-9
		(*b*) Describe any methods used to examine subgroups and interactions	8-9
		(*c*) Explain how missing data were addressed	9
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed	9
		Case-control study—If applicable, explain how matching of cases and controls was addressed	N/A
		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	N/A
		(*e*) Describe any sensitivity analyses	N/A
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10, Flowchart
		(b) Give reasons for non-participation at each stage	Flowchart
		(c) Consider use of a flow diagram	Figure 1 in sup
Descriptive Data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	23-24
		(b) Indicate number of participants with missing data for each variable of interest	N/A
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome Data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	Table 2
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	N/A
		Cross-sectional study—Report numbers of outcome events or summary measures	N/A

Section and Item	Item No.	Recommendation	Reported on Page No.
Main Results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Figure 2
		(*b*) Report category boundaries when continuous variables were categorized	10-12
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Table 2
Other Analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key Results	18	Summarise key results with reference to study objectives	13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-16
Generalisability	21	Discuss the generalisability (external validity) of the study results	13-16
Other Information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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Atrial fibrillation in patients with severe mental disorders and the risk of stroke, and fatal thromboembolic events, and bleeding: a nationwide cohort study

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Secondary Subject Heading:	Mental health
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Atrial fibrillation in patients with severe mental disorders and the risk of stroke, fatal thromboembolic events, and bleeding: a nationwide cohort study

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Running title: Atrial fibrillation outcomes in patients with severe mental disorders

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ABSTRACT

Objectives: Outcomes of atrial fibrillation (AF) in patients with severe mental disorders are largely unknown. We compared rates of stroke, fatal thromboembolic events, and bleeding in AF patients with and without mental disorders.

Design: Nationwide registry-based cohort study.

Setting: Denmark (population 5,6 million), 2000-2015.

Participants: AF patients with schizophrenia (n=534), severe depression (n=400), or bipolar disease (n=569) matched 1:5 on age, sex and calendar time to AF patients without mental disorders.

Exposure: Inpatient or hospital-based outpatient diagnosis of schizophrenia, severe depression or bipolar disease.

Primary and secondary outcome measures: Hazard ratios (HR) for stroke, fatal thromboembolic events, and major bleeding comparing patients with and without mental disorders estimated by Cox regression with sequential adjustment for risk factors for stroke and bleeding, comorbidity, and initiation of oral anticoagulant therapy (OAT).

Results: Compared with matched comparisons, crude 5-year HRs of ischemic stroke was 1.37 (95% confidence intervals (CI) 0.88-2.14) for schizophrenia, 1.36 (95% CI 0.89-2.08) for depression, and 1.04 (95% CI 0.69-1.56) for bipolar disease. After adjusting for risk factors, comorbidity, and OAT these HRs declined toward the null. Crude HRs of fatal thromboembolic events were 3.16 (95% CI 1.78-5.61) for schizophrenia, 1.31 (95% CI 0.67-2.56) for depression, and 1.53 (95% CI 0.93-2.53) for bipolar disease. Rates of major bleeding were increased in patients with schizophrenia (crude HRs 1.37, 95% CI 0.99-1.90) and severe depression (HR 1.25, 95% CI 0.87-1.78) but not bipolar disease (HR 0.82, 95% CI 0.58-1.15).

Conclusion: AF patients with schizophrenia or severe depression experienced increased rates of stroke and major bleeding compared with matched comparisons. This increase were largely

explained by differences in the prevalence of risk factors for stroke and bleeding, comorbidity and initiation of OAT during follow-up. AF patients with schizophrenia also experienced higher mortality following thromboembolic events than matched comparisons without mental disorder.

Keywords: Atrial fibrillation, schizophrenia, depression, bipolar disease, stroke, bleeding, outcome.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The study included all patients with a hospital diagnosis of atrial fibrillation in Denmark in 2000-2015. The study had complete follow-up on all participants from the nationwide Danish Civil Registration System.
- The study was conducted in a government financed healthcare system with equal access for the entire Danish population.
- Despite equal access to tax-supported health care in Denmark, diagnoses in patients with mental disorders may have been underreported.
- The study lacked data on alcohol, smoking, exercise, and other lifestyle related risk factors associated with increased risk of study outcomes. We were able to adjust for hospital diagnoses of alcohol-related conditions and other lifestyle-related diseases, but cannot exclude residual confounding.
- Finally, the data did not contain information on the quality and compliance with oral anticoagulant therapy.

INTRODUCTION

Cardiovascular diseases are highly prevalent in patients with severe mental disorders such as schizophrenia, bipolar disease and severe depression,[1] contributing to a 10-20 year shorter life expectancy than the general population.[2] Potential explanations include a high prevalence of cardiovascular risk factors such as smoking, dyslipidemia, hypertension, diabetes, and obesity.[3–5] In addition, antipsychotic medications may adversely affect cardiovascular disease risk via metabolic pathways involving dyslipidemia, weight gain, and diabetes.[6,7]

Atrial fibrillation (AF) is the most common cardiac arrhythmia, affecting up to 1-2% of the population in developed countries, and confers a substantial increased risk of stroke, heart failure and death.[8] Despite increasing clinical and research focus on cardiovascular diseases in AF patients with mental disorders, the stroke risk in patients with mental disorders is largely unknown. Prior studies have shown that AF patients with mental disorders are less likely to start oral anticoagulant therapy (OAT) than those without,[9,10] and that those who receive OAT have worse anticoagulation control[9,11,12] and increased risk of major haemorrhage.[11,13] However, these studies only assessed outcomes in patients receiving OAT for at least 100-180 days, excluding patients who never initiated therapy and those who discontinued therapy shortly after initiation.[11,13]

We aimed to examine the prognostic importance of severe mental disorders in AF patients. In a nationwide cohort of patients with incident AF, we conceived a matched cohort study to compare the risk of stroke, fatal thromboembolic events, and major bleeding in AF patients with a prior diagnosis of schizophrenia, severe depression or bipolar disease to matched comparison cohorts without these disorders. By sequentially adjusting for stroke risk factors, bleeding risk factors, comorbidity, and use of OAT, we sought to further characterize the association between mental disorders and AF outcomes.

METHODS

Data sources

This cohort study linked three well-established Danish nationwide; the National Patient Register[14], the National Prescription Register[15], and the Civil Registration System.[16] The National Patient Register holds information on dates of admission and discharge, and discharge diagnoses classified according to the *International Classification of Diseases* (ICD) for more than 99% of hospital admissions in Denmark. The Prescription Registry contains data on all prescription purchases by Danish residents since 1995. Data includes the patients' civil registration number, date of dispensing, and type and quantity of drug prescribed. The Danish Person Registry holds data on sex, date of birth, vital and emigration status. The appendix provides information on codes for diagnoses and medications. The registries were linked using the unique personal civil registration number assigned to all Danish residents, allowing a true population-based study covering all 5,6 million inhabitants of Denmark during the study period. We performed all linkages within Statistics Denmark, a governmental institution that collects and processes information for statistical and scientific purposes.[17] The study was approved by the Danish Data Protection Agency (Record number 2012-41-0633). According to Danish law, approval from an ethics committee is not required for anonymous registry-based studies.

Study population

We established a cohort of all patients with incident non-valvular AF, defining non-valvular AF as presence of AF, and baseline absence of mitral stenosis or mechanical heart valves. Specifically, we identified all patients discharged with a first hospital diagnosis of non-valvular AF between 2000 and 2015. To ensure sufficient clinical record history for treatment and diagnoses, we excluded patients who had not been residents in Denmark for at least 1 year before date of AF diagnosis

(index date). We further excluded patients with valvular AF; patients who died on the day of AF diagnosis; and patients with a fatal thromboembolic event defined as death within the following 30 days of ischemic stroke, systemic embolism, pulmonary embolism or myocardial infarction before AF diagnosis (Supplementary Figure 1). The positive predictive value (PPV) of an AF diagnosis in the National Patient Register is 95% (95% CI 89-98).[18]

Exposure

Through the National Patient Register, we identified all patients in the study population with an inpatient or outpatient diagnosis of schizophrenia, bipolar disease or severe depression before the index date. In Denmark, these mental disorders are primarily treated in public hospitals ensuring a high coverage of contacts with psychiatric disorders. The PPV of a diagnosis of mental disorders in the National Patient Register is 98% (95% CI 90-99).[18]

To control for confounding by reducing imbalance in the data and thereby model dependence and bias, we used Coarsened Exact Matching to produce a one-to-five match of patients with schizophrenia, severe depression, or bipolar disease on age, sex and calendar time (year of index date) to comparison cohorts of AF patients without mental disorders.[19] Patients age was grouped in approximately 5-year intervals based on the statistical software package Stata's (Stata Corp, version 14) function *cem*'s algorithm for automatic coarsening.[20] To evaluate the effect of matching on the balance between baseline variables we estimated the absolute standardized differences before and after matching.

Patient characteristics

Baseline comorbidity was defined according to medication claims within the year before the AF diagnosis and/or history of primary or secondary hospital discharge diagnoses (excluding emergency room diagnoses) since 1994. Comorbidity information included cardiovascular and metabolic diseases, and lifestyle related diseases (e.g., alcohol-related diseases such as alcoholic liver disease, and alcoholic polyneuropathy, cardiomyopathy, gastritis or myopathy, and alcohol-induced pancreatitis). We further combined baseline information into the CHA_2DS_2VASc stroke risk score[21] to summarize perceived stroke risk at baseline, and the HAS-BLED score[22] as a measure of bleeding risk at baseline (see score definitions in Supplementary Table 2).

Outcomes

Study outcomes were ischemic stroke, fatal thromboembolic events of ischemic stroke, systemic embolism, pulmonary embolism or myocardial infarction (as defined above), and major bleeding events recorded as intracranial, gastro-intestinal, and major bleeding in various anatomical positions reported in total as 'any bleeding'. We derived all outcomes from hospital diagnoses in the National Patient Register. Stroke diagnoses were required to be primary in-hospital codes, excluding emergency room and ambulatory diagnoses, to ensure higher validity.

Statistical analyses

We followed all patients from their AF diagnosis and up to five years after baseline. Follow-up was censored at time of death, migration, study end (November 21, 2016), or the outcome of interest, whichever came first. Patient baseline characteristics were presented as proportions for discrete variables and means with standard deviations (SD) for continuous variables. Crude incidence rates were calculated as number of events divided by person-time. Cumulative incidence functions (by means of the Aalen-Johansen estimator), assuming death as competing risk, were used to depict risk

of outcome during follow-up. We assessed the association between each mental disorder and study outcome using Cox Proportional hazard regression with stratification on the matched groups. To assess to which extend the observed association could be explained by comorbidity and/or use of OAT, we performed sequential cumulative adjustment for 1) stroke risk and bleeding risk as summarized by components of the CHA_2DS_2VASc and HAS-BLED scores, and comorbidities not included in CHA_2DS_2VASc and HAS-BLED (chronic pulmonary disease, cancer, and venous thromboembolism), and 2) use of OAT during follow-up modelled as a time-varying covariate shifting from untreated to treated status at first observed prescription of any OAC. We excluded age and sex in the CHA_2DS_2VASc and HAS-BLED scores as these were included as matching factors and perfectly balanced between comparison cohorts (Supplementary Table 3). The distribution of time to OAC treatment initiation was presented by cumulative incidence curves (Supplementary Figure 2). Point estimates were reported with 95% confidence intervals (CI) and a p-value less than 0.05 was considered statistically significant.

RESULTS

We identified 260,974 AF patients during the study period. After exclusions, the study cohort comprised 253,741 AF patients of which 534 patients had schizophrenia, 400 severe depression, and 569 bipolar disease (Supplementary Figure 1). Table 1 shows baseline characteristics according to presence and type of mental disorder. AF patients with schizophrenia were substantially younger (mean age 64.5 years) whereas the age of patients with severe depression (73.7 years) and bipolar disease (73.0 years) was comparable with patients without mental disorders (73.3 years). Baseline stroke risk appeared lower in patients with schizophrenia; mean CHA_2DS_2-VASc score was 2.5 versus 3.1 in patients without mental disorders. However, this was explained by the lower age of schizophrenic patients. The CHA_2DS_2-VASc score was 3.6 in patients with severe depression and 3.3 in patients with bipolar disease (Table 1). The higher CHA_2DS_2-VASc score in patients with severe depression was primarily driven by a large proportion of females (61.8% vs. 46.7% in comparisons) and patients with prior stroke (30.3% vs. 16.9%). In comparison, 14.2% of schizophrenic patients had prior stroke; they also had lower prevalence of hypertension, myocardial infarction, and peripheral arterial disease. Compared with patients with no mental disorder, the HAS-BLED score was also higher in patients with severe depression and bipolar disease whereas it was lower in patients with schizophrenia. Alcohol-related diseases were prevalent across all mental disorders, particularly for patients with schizophrenia or bipolar disease (~20% vs. 4% in comparisons). Supplemental Table 3 shows characteristics for patients with schizophrenia, severe depression, and bipolar disease and their matched comparisons. After matching, the mean CHA_2DS_2-VASc score was 2.3 in AF patients without schizophrenia (Supplementary Table 3).

Ischemic stroke

Figure 1 displays cumulative incidence curves for ischemic stroke in the matched cohorts. Rates of ischemic stroke at 5 years was 1.96 events per 100 person-years in schizophrenic AF patients vs.

1.30 in matched comparisons (Table 2), yielding a crude HR of 1.37 (95% CI 0.88-2.14) with confidence intervals including unity (Figure 2). After adjustment for stroke risk as summarized by the CHA_2DS_2-VASc and HAS-BLED scores and other comorbidities this HR was 1.29 (95% CI 0.81-2.07) (Figure 2). Rates of OAT initiation in AF patients with mental disorders was substantially lower than in matched comparisons (Supplementary Figure 2), and after additional adjustment for OAT use during follow-up the HR of ischemic stroke was 1.16 (95% CI 0.72-1.87) (Figure 2). At 5-years the rate of ischemic stroke was 2.74 per 100 person-years in patients with severe depression vs. 1.93 in matched comparisons (crude HR of 1.36, 95% CI 0.89-2.08). Similar to patients with schizophrenia, the crude HR was substantially attenuated by sequential adjustment for stroke risk factors, comorbidity, and OAT (HR 1.01, 95% CI 0.64-1.58) (Figure 2). This pattern of diminishing HRs with sequential adjustment for stroke risk factors and OAT was also evident in patients with bipolar disease in whom the crude HR was 1.04 (95% CI 0.69-1.56) and the fully adjusted HR was 0.85 (95% CI 0.55-1.29). Thus, compared with AF patients without mental disorders, the fully adjusted HRs indicated comparable HRs of ischemic stroke across all mental disorders with wide CIs that crossed unity (Figure 2).

Fatal thromboembolic events

During 5-years follow-up, 19 fatal thromboembolic events occurred in AF patients with schizophrenia, 11 in patients with severe depression and 20 in patients with bipolar disease. Accordingly, rates of fatal thromboembolic events per 100 person-years was substantially lower than rates of ischemic stroke; 1.43 for schizophrenia vs. 0.52 in matched comparisons, 1.03 vs. 0.82 for severe depression, and 1.41 vs. 0.83 for patients with bipolar disease (Table 2). Notwithstanding, due to the low rate in the matched comparisons, cumulative incidence curves

revealed distinct differences in rates of fatal thromboembolic events in patients with schizophrenia vs. matched comparisons (Figure 3) and to lesser extent in patients with bipolar disease. The equivalent 5-year HR was 3.16 (95% CI 1.78-5.61) decreasing to 2.88 (95% CI 1.57-5.28) after adjustment for stroke risk factors, comorbidity, and OAT (Figure 2). The unadjusted HR of fatal thromboembolic events in patients with severe depression vs. matched comparisons was 1.31 (95% CI 0.67-2.56). After adjustment for stroke risk factors, comorbidity, and OAT, the HR was 0.75 (95% CI 0.37-1.52). In patients with bipolar disease the crude HR was 1.53 (95% CI 0.93-2.53) compared with matched comparisons. Following sequential adjustment the HR was 1.23 (95% CI 0.72-2.09) (Figure 2).

Major bleeding

The cumulative incidence curves showed higher rates of major bleeding in patients with schizophrenia and severe depression compared with their matched comparisons, whereas the curves for bipolar disease overlapped (Figure 4). At 5 years, the rate of bleeding was 3.72 events per 100 person-years in schizophrenic patients vs. 2.62 in matched comparisons (crude HR of 1.37, 95% CI 0.99-1.90), 4.06 per 100 person-years in patients with severe depression vs. 3.24 in matched comparisons (crude HR of 1.25, 95% CI 0.87-1.78), and 2.90 vs. 3.27 in patients with bipolar disease (HR of 0.82, 95% CI 0.58-1.15) (Table 2, Figure 2). Sequential adjustment for the components of the CHA_2DS_2-VASc and HAS-BLED scores (including use of aspirin, NSAID and clopidogrel at baseline) and use of OAT attenuated the association in patients with schizophrenia and severe depression (Figure 2).

DISCUSSION

Principal findings

This nationwide cohort study revealed a low prevalence of severe mental disorders among patients with incident AF in Denmark. Patients with schizophrenia or severe depression experience higher risk of ischemic stroke and major bleeding compared with matched AF patients without mental disorders, although the differences were not statistically significant. However, after sequential adjustment for stroke and bleeding risk factors, comorbidity and use of OAT, hazard rates were comparable with matched comparisons, suggesting that the excess risk in patients with schizophrenia and severe depression stem from higher prevalence of risk factors for stroke and bleeding and differences in use of OAT. In comparison, bipolar disease was not associated with higher risk of stroke and bleeding both before and after adjustment. Few thromboembolic events occurred during follow-up. Nonetheless, we noted a substantially higher mortality after a thromboembolic event in patients with schizophrenia than in matched comparisons.

Strengths and limitations

These estimates of stroke risk and thromboembolic events in AF patients are based on a nationwide cohort study conducted in a setting where virtually all medical care is provided free of charge, and with complete follow-up through nationwide registries. Nonetheless, despite universal tax-supported health care in Denmark, diagnoses in patients with mental disorders may have been underreported.[23,24] From the current study, we are not able to conclude whether the low prevalence of AF patients with mental disorders reflect the true picture or whether AF may be under-diagnosed in these patients. Likewise, we cannot exclude a possibility for differential misclassification of study outcomes, if stroke and thromboembolic events were under-diagnosed in patients with severe mental disorders. Such misclassification would bias our estimates toward the null. Furthermore, we included only patients with mental disorders recorded in the hospital register, and the prevalence is likely underestimated, mainly with regard to severe depression. However, we infer that the majority

of patients with schizophrenia and bipolar disease are in contact with the psychiatric hospital system due the severity of these conditions. It is also important to note that we only had information on psychiatric admissions from 1995 onwards. Thus, patients with a diagnosis before 1995 and no recorded diagnosis thereafter would not be included in the exposed cohort. Lack of data on alcohol, smoking, exercise, and other lifestyle related risk factors associated with increased risk of study outcomes is another limitation. We were able to adjust for hospital diagnoses of alcohol-related conditions and many other lifestyle-related diseases including chronic pulmonary disease, diabetes, liver disease, cardiovascular disease, and cancer, which were more prevalent among patients with mental disorders. Nonetheless, incomplete control for these factors likely lead to residual confounding, e.g. bleeding risk due to alcohol abuse.[25,26] Likewise, we did not assess the association between anti-psychotic medications and stroke risk in this study. Finally, Use of OAT was determined based on prescription redemption, which may be a limitation, as some patients may not take their medication. Our data did not contain information on the quality and compliance with OAT, which may be lower among patients with mental disorders due to cognitive limitations and maladaptive behaviours.[27]

Comparison with other studies

Our findings are concordant with two prior studies on outcomes of AF patients with mental disorders receiving warfarin.[11,13] In a US cohort study of 9,345 Medicaid recipients receiving two or more warfarin prescriptions less than 100 days apart, Schauer et al[13] demonstrated HRs of 1.36 (95% CI 1.06-1.74) for ischemic stroke in patients with mental disorders illnesses compared with patients without. In another US cohort study, Paradise et al[11] showed that mental disorders was associated with an increased risk of major bleeding (HR:1.19, 95% CI 1.11-1.27) in patients with any mental disorder vs. propensity matched comparisons in 103,897 patients receiving warfarin for

at least 6 months through the Veterans Health Administration. Both studies only included patients who were considered appropriate for OAT and who actually received it and remained successfully on treatment for an extended period. Thus, these results may not reflect stroke risk in all patients with mental disorders.

Our findings expand prior studies by including all AF patients regardless of OAT use. We saw a noticeable lower rate of OAT initiation in patients with mental disorders compared with matched comparisons, which is in line with prior studies showing that AF patient with mental disorders are less likely to receive OAT.[9,10] Schmitt et al[10] found that AF patients with mental disorders had higher prevalence of stroke risk factors and contraindications to OAT. Thus, lower treatment rates in patients with mental disorders may reflect appropriate attention to bleeding risk. On the other hand, when restricting to patients eligible for OAT, patients with mental disorders remained less likely to receive OAT.[10] As the higher stroke rates in our study appeared to be due to differences in stroke risk factors, comorbidity, and receipt of OAT, any disparities in the care of AF patients with mental disorders requires close attention. Other studies have shown that patients with mental disorders have worse OAT control.[9,11,12] Walker et al[9] found that when prescribed warfarin, AF patients with mental disorders were substantially more likely to have highly supra-therapeutic International Normalized Ratio (INR) values than those without mental disorders (27.3% vs. 1.6% had at least one INR measurement above 5.0). However, this assessment was based on a sub-cohort of only 84 AF patients and should be interpreted with caution.

The higher mortality within the 30-days following a thromboembolic event in patients with schizophrenia is of concern and emphasizes the need for vigilant follow-up in this patient population. The finding is in line with prior studies reporting increased cardiac mortality in patients

with schizophrenia.[24,28] Future studies are encouraged to explore potential reasons which are likely multifactorial and may entail both severity of illness, comorbidity, quality of care, and factors beyond patient care.[29]

Conclusions

In conclusion, this study showed that schizophrenia or severe depression in patients with AF is associated with increased risk of ischemic stroke and major bleeding. When sequentially controlling for stroke and bleeding risk factors, comorbidity, and use of OAT the hazard rates attenuated and were comparable with matched comparisons, indicating that the excess risk is due to a higher prevalence of risk factors for stroke and bleeding and lower use of OAT in patients with mental disorders. In comparison, rates were not increased in patients with bipolar disease when compared with age and sex matched comparisons without mental disorders both before and after adjustment. Patients with schizophrenia also experienced higher mortality following a thromboembolic event than matched comparisons. These findings highlight the importance of close attention to stroke and bleeding risk factors and potential disparities in receipt of OAT in AF patients with mental disorders. Our findings also identify challenges in the management of AF patients with mental disorders; the excess burden of stroke risk factors signifies the need for stroke prevention whereas the higher rates of major bleeding emphasize that that cautious assessment of bleeding risk and quality of OAT may be particularly pertinent for patients with mental disorders. In this respect, our findings could indicate a need for optimized coordination and collaboration between general somatic and mental health services in order to optimize treatment.

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Author Contributions

MS, FS and JNK had full access to all of the data in this study and take responsibility for the integrity of the data and the accuracy of the data analysis. SR, SPJ and TBL provided the idea for the study. MS, FS, TBL and SR defined the study concept and performed the critical interpretation of the data. MS drafted the article. All authors contributed critical revisions and approved the final version to be published.

Conflicts of Interest Disclosures

Associate Professor Larsen has served as an investigator for Janssen Scientific Affairs, LLC and Boehringer Ingelheim and has served as a speaker for Bayer, BMS/Pfizer, Boehringer Ingelheim. Senior Statistician Flemming Skjøth has served as a consultant for Bayer. Other authors – none declared.

Role of the Funders/Sponsors

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Ethics approval: The study was approved by the Danish Data Protection Agency (Record number 2012-41-0633).

Data sharing statement: No additional data are available

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FIGURE LEGENDS

Figure 1. Cumulative incidence of ischemic stroke in patients with atrial fibrillation and mental disorders and matched atrial fibrillation patients without mental disorders.

Figure 2. Crude and adjusted hazard ratios (HR) with 95% confidence intervals (CI) for ischemic stroke, fatal thromboembolic events, and major bleeding in atrial fibrillation patients with severe mental disorders compared with matched atrial fibrillation patients without mental disorders.

Figure 3. Cumulative incidence of fatal thromboembolic events in patients with atrial fibrillation and mental disorders and matched atrial fibrillation patients without mental disorder.

Figure 4. Cumulative incidence of major bleeding in patients with atrial fibrillation and mental disorders and matched atrial fibrillation patients without mental disorder.

Table 1. Descriptive characteristics of patients with incident atrial fibrillation in Denmark according to presence of mental health disorders before matching.

Characteristic, % (N)	No mental disorder (N=252,238)	Schizophrenia (N=534)	Severe depression (N=400)	Bipolar disease (N=569)
Demographic characteristics				
Females	46.7 (117,876)	45.7 (244)	61.8 (247)	59.6 (339)
Mean age (SD)	73.3 (13.1)	64.5 (13.7)	73.7 (14.0)	73.0 (11.2)
Stroke risk factors and comorbidity				
Mean CHA_2DS_2VASc score (SD)	3.1 (1.8)	2.5 (1.7)	3.6 (2.0)	3.3 (1.8)
Mean HASBLED score (SD)	2.2 (1.2)	1.9 (1.3)	2.5 (1.4)	2.5 (1.3)
Prior stroke	16.9 (42,585)	14.2 (76)	30.3 (121)	20.2 (115)
Heart failure	25.7 (64704)	30.0 (160)	30.3 (121)	29.3 (167)
Hypertension	42.6 (107,332)	26.6 (142)	44.5 (178)	36.6 (208)
Myocardial infarction	10.3 (26,089)	8.2 (44)	11.3 (45)	9.3 (53)
Peripheral arterial disease	7.6 (19,266)	6.7 (36)	10.0 (40)	9.0 (51)
Diabetes	12.9 (32,606)	24.3 (130)	15.8 (63)	20.2 (115)
Prior bleeding	26.4 (66,694)	28.1 (150)	44.0 (176)	37.6 (214)
Renal dysfunction	5.2 (13,003)	10.1 (54)	8.5 (34)	15.8 (90)
Prior venous thromboembolism	4.8 (12,081)	7.3 (39)	10.8 (43)	10.0 (57)
Chronic pulmonary disease	14.5 (36,615)	28.7 (153)	22.3 (89)	30.8 (175)
Cancer	15.9 (40,171)	12.9 (69)	14.8 (59)	17.0 (97)
Alcohol-related disease	4.2 (10,471)	19.1 (102)	11.0 (44)	20.9 (119)
Medication use within 365 days before index date				
Coumarin	14.4 (36,326)	5.1 (27)	8.8 (35)	12.1 (69)
NOAC	2.5 (6,347)	3.4 (18)	2.3 (9)	2.3 (13)
Aspirin	37.6 (94,951)	33.0 (176)	40.5 (162)	38.1 (217)
Clopidogrel	4.3 (10,936)	5.6 (30)	9.0 (36)	5.6 (32)
NSAID	26.7 (67,468)	25.1 (134)	27.3 (109)	25.0 (142)

Digoxin	12.4 (31,200)	9.9 (53)	8.8 (35)	12.1 (69)
Non-loop diuretics	36.2 (91,336)	25.1 (134)	38.8 (155)	34.4 (196)
Loop-diuretics	25.5 (64,337)	34.8 (186)	28.8 (115)	36.0 (205)
Beta-blocker	32.2 (81,335)	22.7 (121)	28.0 (112)	24.3 (138)
Calcium channel blocker	25.5 (64,355)	17.0 (91)	31.0 (124)	25.1 (143)
Renin-angiotensin inhibitor	35.5 (89,621)	23.8 (127)	37.5 (150)	32.0 (182)
Statins	24.6 (62,166)	23.2 (124)	26.0 (104)	27.4 (156)
Antiepileptics	4.0 (10,077)	24.3 (130)	16.0 (64)	39.5 (225)
Anticholinergics	0.2 (456)	27.2 (145)	2.3 (9)	5.3 (30)
Antipsychotics, lithium and anxiolytics/hypnotics	27.1 (68,302)	87.1 (465)	63.2 (253)	83.3 (474)
Antidepressants	14.5 (36,516)	34.8 (186)	78.5 (314)	61.0 (347)

Abbreviations:
SD: Standard deviation
NOAC: Non-vitamin K oral anticoagulant
NSAID: Non-steroidal anti-inflammatory drugs

Table 2. Number of events and rates of stroke, fatal thromboembolic events, and major bleeding at 5 years following incident atrial fibrillation.

Characteristic	Patients	Ischemic stroke		Fatal thromboembolic events		Major bleeding	
	N	Events, N	Rate	Events, N	Rate	Events, N	Rate
Entire unmatched AF comparison cohort	252,238	15,710	2.03	8,039	1.00	26,711	3.53
Schizophrenia							
Schizophrenia	534	25	1.96	19	1.43	46	3.72
Matched comparison cohort	2,669	114	1.30	47	0.52	225	2.62
Severe depression							
Severe depression	400	28	2.74	11	1.03	41	4.06
Matched comparison cohort	2,000	113	1.93	50	0.82	188	3.24
Bipolar disease							
Bipolar disease	569	28	1.90	20	1.41	39	2.90
Matched comparison cohort	2,845	164	2.04	74	0.83	274	3.27

Rates are calculated as number of events divided by person-time per 100 years.

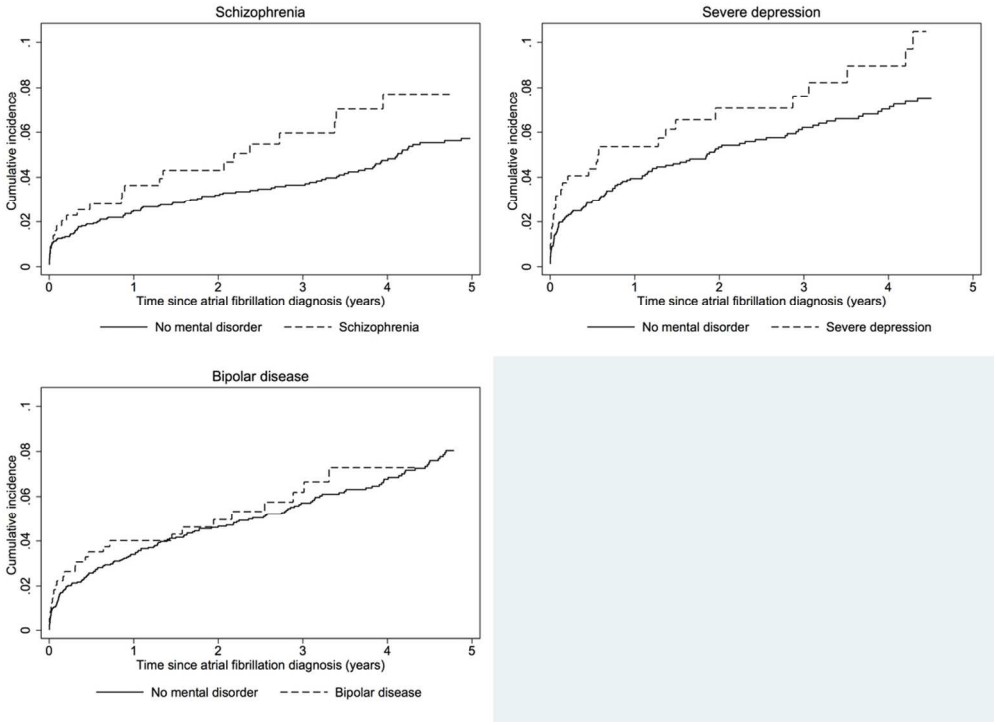

Figure 1

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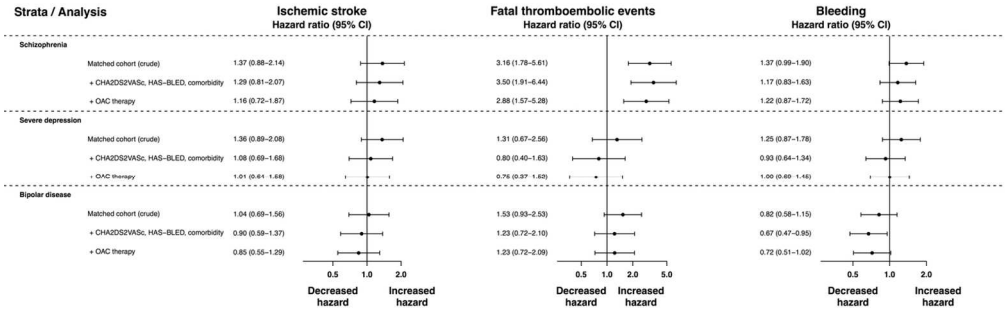

Figure 2

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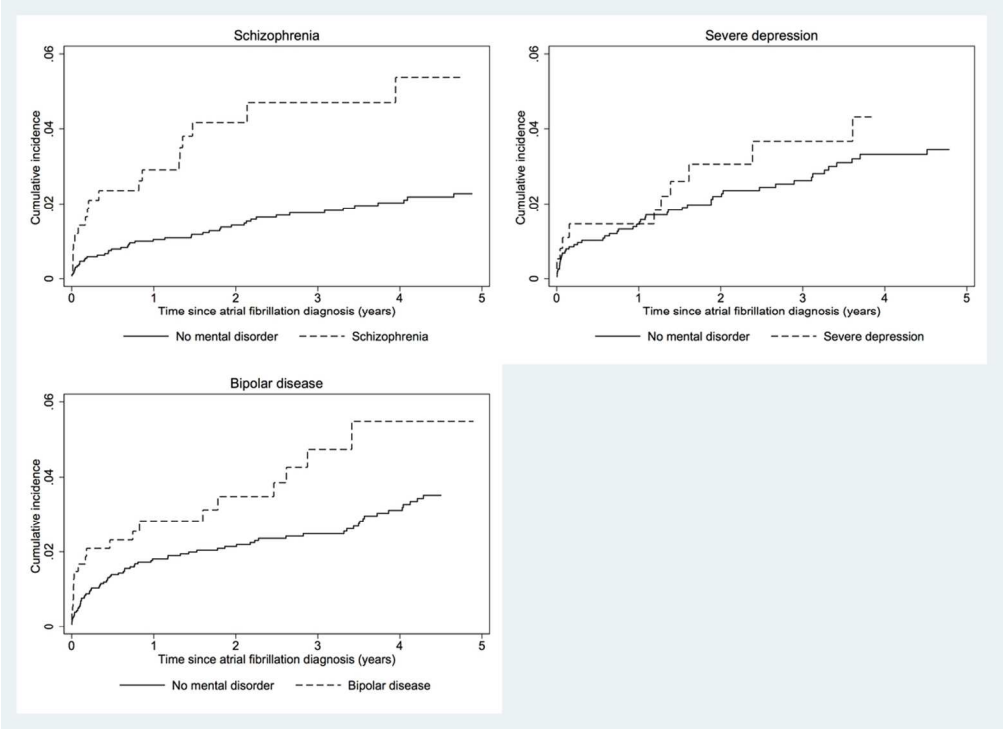

Figure 3

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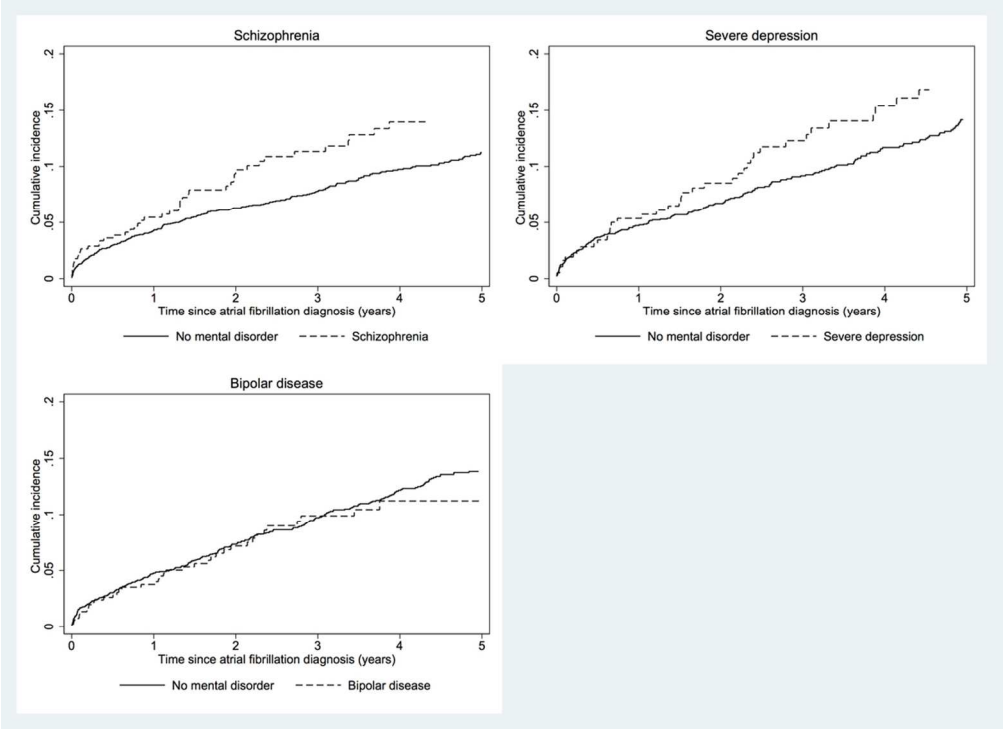

Figure 4

101x73mm (300 x 300 DPI)

SUPPLEMENTAL INFORMATION

Atrial fibrillation in patients with severe mental disorders and the risk of stroke, fatal thromboembolic events, and bleeding: a nationwide cohort study

Mette Søgaard,PhD[1,2], Flemming Skjøth, PhD[2,3], Jette Nordstrom Kjældgaard[1,2], BSCEE, Torben Bjerregaard Larsen, PhD[1,2,5], Søren Pihlkjær Hjortshøj, PhD[4,5], Sam Riahi, PhD[1,4,5]

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Supplementary tables and figures

Supplementary Table 1. Definitions on comorbidity, concomitant medication, and study outcomes according to ICD-10 codes and ATC-codes.

Diagnoses	International Classification of Diseases 10th revision (ICD-10) code	Anatomical Therapeutic Chemical (ATC) code
Study population		
Atrial fibrillation	I48	
Exposure		
Schizophrenia	F20	
Bipolar disease	F30 F31	
Severe depression	F322 F323 F332 F333	
Outcomes		
Ischemic stroke	I63 I64	
Major bleeding	I60 I61 I62 K250 K252 K254 K260 K262 K264 K270 K272 K274 K280 K282 K290 K920 K921 K922 D62 J942 H113 H356 H431 N02 R04 R31 R58	
Thromboembolic events		
Ischemic stroke	I63 I64	
Systemic embolism	I74	
Pulmonary embolism	I26	
Myocardial infarction	I21 I23	
Baseline covariates		
Heart failure	I110 I130 I132 I420 I50	
Hypertension		See specified definition[a]
Peripheral vascular/ischemic disease	I702 I703 I704 I705 I706 I707 I708 I709 I71 I739	
Diabetes	E100 E101 E109 E110 E111 E119	A10
Prior bleeding	K250 K252 K254 K260 K262 K264 K270 K272 K274 K280	

	K282 K290 K920 K921 K922 D62 J942 H113 H356 H431 N02 R04 R31 R58	
Renal dysfunction	I12 I13 N00 N01 N02 N03 N04 N05 N07 N11 N14 N17 N18 N19 Q61	
Prior VTE	I801 I802 I803 I808 I809 I819 I636 I676 I822 I823 I828 I829	
Chronic pulmonary disease	J40 J41 J42 J43 J44 J45 J46 J47 J60 J61 J62 J63 J64 J65 J67 J684 J701 J703 J841 J920 J961 J982 J983	
Cancer	C	
Alcohol-related disease	E224 E529A F10 G312 G621 G721 I426 K292 K70 K860 L278A O354 T51 Z714 Z721	
Medications within 365 days before index date		
Coumarin		B01AA
NOAC		B01AF01 B01AF02 B01AE07
Aspirin		B01AC06
Clopidogrel		B01AC04
NSAID		M01A
Digoxin		C01AA05
Non-loop diuretics		C02DA C02L C03A C03B C03D C03E C03X C07C C07D C08G C09BA C09DA C09XA52
Loop-diuretics		C03C
Beta-blocker		C07
Calcium channel blocker		C07F C08 C09BB C09DB
Renin-angiotensin inhibitor		C09
Statins		C10

Abbreviations: VTE, venous thromboembolism; NOAC, Non-vitamin K oral anticoagulant; NSAID, Non-steroidal anti-inflammatory drugs.

[a]We identified subjects with hypertension from combination treatment with at least two of the following classes of antihypertensive drugs:

I· Alpha adrenergic blockers (C02A, C02B, C02C)

II· Non-loop diuretics (C02DA, C02L, C03A, C03B, C03D, C03E, C03X, C07C, C07D, C08G, C09BA, C09DA, C09XA52)

III· Vasodilators (C02DB, C02DD, C02DG, C04, C05)

IV· Beta blockers (C07)

V· Calcium channel blockers (C07F, C08, C09BB, C09DB)

VI· Renin-angiotensin system inhibitors (C09)

Supplementary Table 2. Risk score definitions.

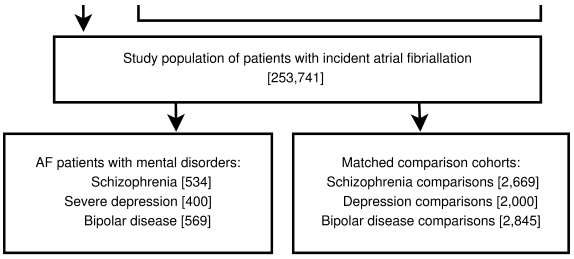
Risk score	Points if present
CHA_2DS_2VASc[a]	
Congestive heart failure or Left Ventricular Dysfunction	1
Hypertension	1
Age ≥ 65 years	1
Age ≥ 75 years	1
Diabetes mellitus	1
Stroke (ischemic stroke, transient ischemic disease or systemic embolism)	2
Vascular disease (myocardial infarction, peripheral arterial disease, or aortic plaque)	1
Sex category (female)	1
HAS-BLED[b]	
Hypertension	1
Abnormal renal function	1
Abnormal hepatic function	1
Stroke (ischemic stroke or transient ischemic attack)	1
Bleeding	1
Labile international normalized ratio[c]	1
Elderly age (≥ 65 years)	1
Drugs (aspirin, clopidogrel, or non-steroidal anti-inflammatory drugs)	1
Alcohol intake	1

[a]Reflects stroke risk in atrial fibrillation patients not in anticoagulant therapy (Lip GYH, Nieuwlaat R, Pisters R, Lane DA, Crijns HJGM. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. Chest 2010;137(2):263-72)

[b]Reflects bleeding risk in atrial fibrillation patients undergoing anticoagulant therapy (Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJGM, Lip GYH. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. Chest 2010;138(5):1093-100).

[c]Not included due to unavailable information

Supplementary Figure 1. Flowchart of the study population.



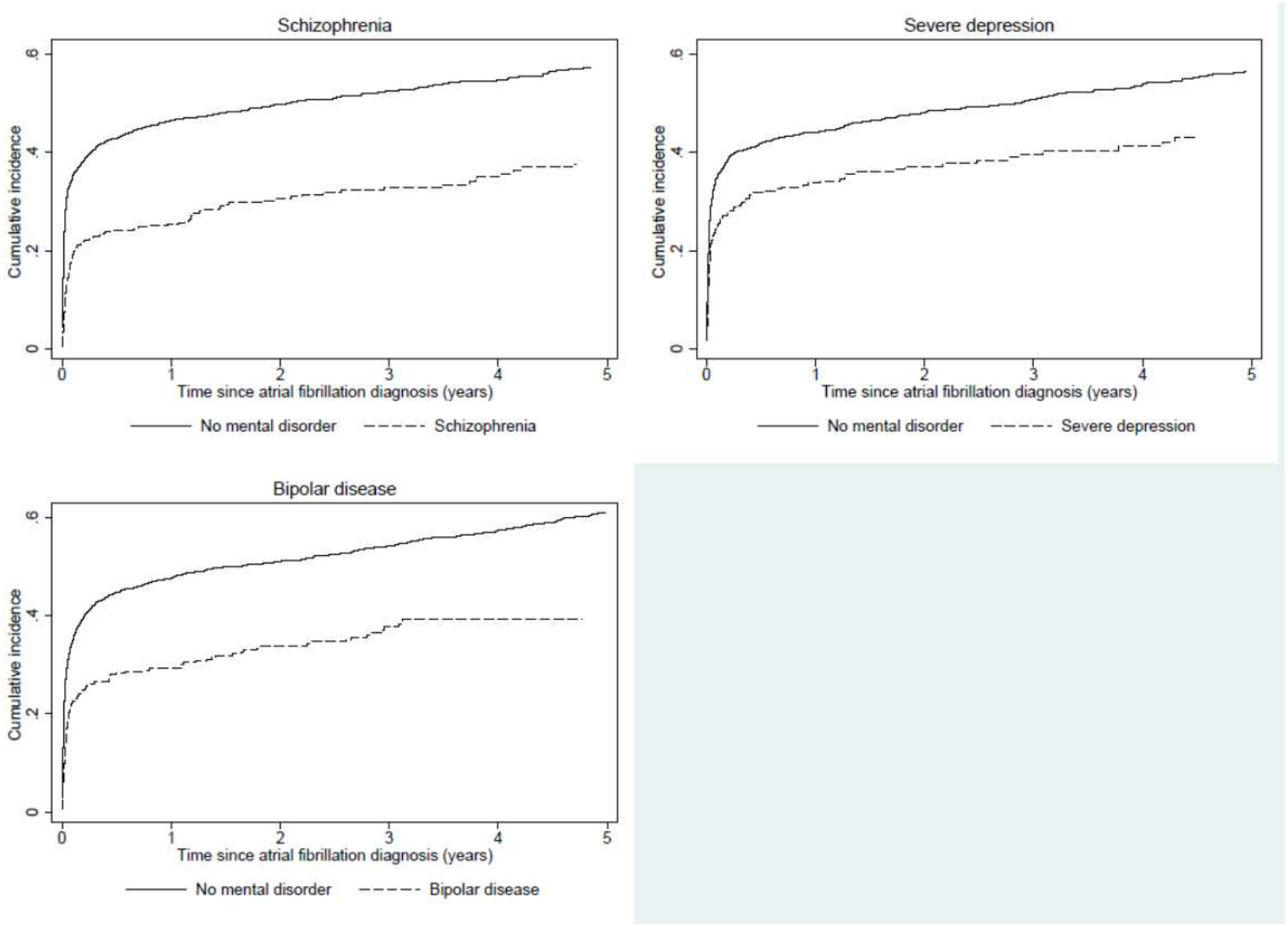
Supplementary Table 3. Descriptive characteristics of AF patients with schizophrenia, severe depression, or bipolar disease and their matched comparison cohorts.

Characteristic, % (N)	Schizophrenia		Severe depression		Bipolar disease	
	Matched AF comparisons	Schizophrenia	Matched AF comparisons	Severe depression	Matched AF comparisons	Bipolar disease
Total number	2,669	534	2,000	400	2,845	569
Females	45.7 (1,219)	45.7 (244)	61.8 (1,235)	61.8 (247)	59.6 (1,695)	59.6 (339)
Mean age (SD)	64.5 (13.7)	64.5 (13.7)	73.5 (14.0)	73.7 (14.0)	73.1 (11.2)	73.0 (11.2)
Mean CHA_2DS_2VASc score (SD)	2.3 (1.8)	2.5 (1.7)	3.3 (1.8)	3.6 (2.0)	3.2 (1.8)	3.3 (1.8)
Mean HASBLED score (SD)	1.8 (1.3)	1.9 (1.3)	2.2 (1.2)	2.5 (1.4)	2.2 (1.2)	2.5 (1.3)
Prior stroke	13.3 (355)	14.2 (76)	17.9 (358)	30.3 (121)	17.8 (505)	20.2 (115)
Heart failure	19.4 (518)	30.0 (160)	23.4 (469)	30.3 (121)	25.3 (720)	29.3 (167)
Hypertension	38.6 (1030)	26.6 (142)	44.1 (882)	44.5 (178)	45.2 (1287)	36.6 (208)
Myocardial infarction	6.9 (185)	8.2 (44)	10.7 (213)	11.3 (45)	9.6 (273)	9.3 (53)
Peripheral arterial disease	5.7 (152)	6.7 (36)	8.1 (161)	10.0 (40)	7.1 (201)	9.0 (51)
Diabetes	12.9 (344)	24.3 (130)	12.9 (259)	15.8 (63)	12.6 (358)	20.2 (115)
Prior bleeding	13.0 (346)	28.1 (150)	15.4 (307)	24.0 (96)	14.4 (409)	23.0 (131)
Renal dysfunction	4.8 (127)	10.1 (54)	4.1 (82)	8.5 (34)	5.1 (144)	15.8 (90)
Prior venous thromboembolism	4.8 (128)	7.3 (39)	5.9 (119)	10.8 (43)	4.7 (135)	10.0 (57)
Chronic pulmonary disease	13.3 (355)	28.7 (153)	14.9 (299)	22.3 (89)	16.1 (458)	30.8 (175)
Cancer	12.9 (345)	12.9 (69)	17.9 (357)	14.8 (59)	17.3 (493)	17.0 (97)
Alcohol-related disease	5.9 (158)	19.1 (102)	3.6 (73)	11.0 (44)	4.3 (122)	20.9 (119)

Coumarin	13.3 (356)	5.1 (27)	13.7 (273)	8.8 (35)	14.3 (407)	12.1 (69)
NOAC	3.7 (99)	3.4 (18)	2.8 (56)	2.3 (9)	3.4 (98)	2.3 (13)
Aspirin	29.6 (790)	33.0 (176)	37.2 (744)	40.5 (162)	37.7 (1073)	38.1 (217)
Clopidogrel	4.3 (116)	5.6 (30)	5.3 (106)	9.0 (36)	5.0 (143)	5.6 (32)
NSAID	27.1 (722)	25.1 (134)	27.1 (542)	27.3 (109)	26.2 (745)	25.0 (142)
Digoxin	6.8 (182)	9.9 (53)	9.3 (187)	8.8 (35)	10.7 (304)	12.1 (69)
Non-loop diuretics	31.4 (839)	25.1 (134)	38.2 (764)	38.8 (155)	38.3 (1089)	34.4 (196)
Loop-diuretics	18.7 (500)	34.8 (186)	24.4 (488)	28.8 (115)	23.7 (675)	36.0 (205)
Beta-blocker	31.4 (837)	22.7 (121)	33.8 (676)	28.0 (112)	34.4 (980)	24.3 (138)
Calcium channel blocker	22.1 (591)	17.0 (91)	27.1 (543)	31.0 (124)	26.5 (753)	25.1 (143)
Renin-angiotensin inhibitor	34.2 (914)	23.8 (127)	37.0 (741)	37.5 (150)	39.2 (1115)	32.0 (182)
Statins	26.4 (704)	23.2 (124)	26.6 (531)	26.0 (104)	28.3 (804)	27.4 (156)
Antiepileptics	3.6 (95)	24.3 (130)	4.7 (94)	16.0 (64)	4.5 (129)	39.5 (225)
Anticholinergics	<4	<4	0.2 (4)	2.3 (9)	0.1 (4)	5.3 (30)
Antipsychotics, lithium and anxiolytics/hypnotics	21.4 (571)	87.1 (465)	26.6 (532)	63.2 (253)	28.8 (820)	83.3 (474)
Antidepressants	14.1 (375)	34.8 (186)	16.1 (323)	78.5 (314)	15.9 (453)	61.0 (347)

Abbreviations:
SD: Standard deviation
NOAC: Non-vitamin K oral anticoagulant
NSAID: Non-steroidal anti-inflammatory drugs

Supplementary Figure 2. Cumulative incidence curves of initiation of oral anticoagulation therapy in age, sex and calendar time matched atrial fibrillation patients with and without mental disorders.



STROBE (Strengthening The Reporting of OBservational Studies in Epidemiology) Checklist

A checklist of items that should be included in reports of observational studies. You must report the page number in your manuscript where you consider each of the items listed in this checklist. If you have not included this information, either revise your manuscript accordingly before submitting or note N/A.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Section and Item	Item No.	Recommendation	Reported on Page No.
Title and Abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/Rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study Design	4	Present key elements of study design early in the paper	1, 2, 5, 6-9
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-9
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6
		Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	N/A
		Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants	N/A
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed	7
		Case-control study—For matched studies, give matching criteria and the number of controls per case	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-9

Section and Item	Item No.	Recommendation	Reported on Page No.
Data Sources/ Measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-9
Bias	9	Describe any efforts to address potential sources of bias	7-9
Study Size	10	Explain how the study size was arrived at	6-7
Quantitative Variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-9
Statistical Methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8-9
		(*b*) Describe any methods used to examine subgroups and interactions	8-9
		(*c*) Explain how missing data were addressed	9
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	9 N/A N/A
		(*e*) Describe any sensitivity analyses	N/A
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10, Flowchart
		(b) Give reasons for non-participation at each stage	Flowchart
		(c) Consider use of a flow diagram	Figure 1 in sup
Descriptive Data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	23-24
		(b) Indicate number of participants with missing data for each variable of interest	N/A
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome Data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	Table 2
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	N/A
		Cross-sectional study—Report numbers of outcome events or summary measures	N/A

Section and Item	Item No.	Recommendation	Reported on Page No.
Main Results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Figure 2
		(*b*) Report category boundaries when continuous variables were categorized	10-12
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Table 2
Other Analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key Results	18	Summarise key results with reference to study objectives	13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-16
Generalisability	21	Discuss the generalisability (external validity) of the study results	13-16
Other Information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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BMJ Open

Atrial fibrillation in patients with severe mental disorders and the risk of stroke, and fatal thromboembolic events, and bleeding: a nationwide cohort study

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Secondary Subject Heading:	Mental health
Keywords:	Atrial fibrillation, Schizophrenia & psychotic disorders < PSYCHIATRY, Depression & mood disorders < PSYCHIATRY, bipolar disease, Stroke medicine < INTERNAL MEDICINE, outcome

Atrial fibrillation in patients with severe mental disorders and the risk of stroke, fatal thromboembolic events, and bleeding: a nationwide cohort study

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Running title: Atrial fibrillation outcomes in patients with severe mental disorders

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ABSTRACT

Objectives: Outcomes of atrial fibrillation (AF) in patients with severe mental disorders are largely unknown. We compared rates of stroke, fatal thromboembolic events, and bleeding in AF patients with and without mental disorders.

Design: Nationwide registry-based cohort study.

Setting: Denmark (population 5,6 million), 2000-2015.

Participants: AF patients with schizophrenia (n=534), severe depression (n=400), or bipolar disease (n=569) matched 1:5 on age, sex and calendar time to AF patients without mental disorders.

Exposure: Inpatient or hospital-based outpatient diagnosis of schizophrenia, severe depression or bipolar disease.

Primary and secondary outcome measures: Hazard ratios (HR) for stroke, fatal thromboembolic events, and major bleeding comparing patients with and without mental disorders estimated by Cox regression with sequential adjustment for risk factors for stroke and bleeding, comorbidity, and initiation of oral anticoagulant therapy (OAT).

Results: Compared with matched comparisons, crude 5-year HRs of ischemic stroke was 1.37 (95% confidence intervals (CI) 0.88-2.14) for schizophrenia, 1.36 (95% CI 0.89-2.08) for depression, and 1.04 (95% CI 0.69-1.56) for bipolar disease. After adjusting for risk factors, comorbidity, and OAT these HRs declined toward the null. Crude HRs of fatal thromboembolic events were 3.16 (95% CI 1.78-5.61) for schizophrenia, 1.31 (95% CI 0.67-2.56) for depression, and 1.53 (95% CI 0.93-2.53) for bipolar disease. Rates of major bleeding were increased in patients with schizophrenia (crude HRs 1.37, 95% CI 0.99-1.90) and severe depression (HR 1.25, 95% CI 0.87-1.78) but not bipolar disease (HR 0.82, 95% CI 0.58-1.15).

Conclusion: AF patients with schizophrenia or severe depression experienced increased rates of stroke and major bleeding compared with matched comparisons. This increase was largely

explained by differences in the prevalence of risk factors for stroke and bleeding, comorbidity and initiation of OAT during follow-up. AF patients with schizophrenia further experienced higher mortality following thromboembolic events than matched comparisons without mental disorders.

Keywords: Atrial fibrillation, schizophrenia, depression, bipolar disease, stroke, bleeding, outcome.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The study included all patients with a hospital diagnosis of atrial fibrillation in Denmark in 2000-2015. The study had complete follow-up on all participants from the nationwide Danish Civil Registration System.
- The study was conducted in a government financed healthcare system with equal access for the entire Danish population.
- Despite equal access to tax-supported health care in Denmark, diagnoses in patients with mental disorders may have been underreported.
- The study lacked data on alcohol consumption, smoking, exercise, and other lifestyle related risk factors associated with increased risk of study outcomes. We were able to adjust for hospital diagnoses of alcohol-related conditions and other lifestyle-related diseases, but cannot exclude residual confounding.
- Finally, the data did not contain information on quality and compliance with oral anticoagulant therapy.

INTRODUCTION

Cardiovascular diseases are highly prevalent in patients with severe mental disorders such as schizophrenia, bipolar disease and severe depression,[1] contributing to a 10-20 year shorter life expectancy than the general population.[2] Potential explanations include a high prevalence of cardiovascular risk factors such as smoking, dyslipidemia, hypertension, diabetes, and obesity.[3–5] In addition, antipsychotic medications may adversely affect cardiovascular disease risk via metabolic pathways involving dyslipidemia, weight gain, and diabetes.[6,7]

Atrial fibrillation (AF) is the most common cardiac arrhythmia, affecting up to 1-2% of the population in developed countries, and confers a substantial increased risk of stroke, heart failure and death.[8] Despite increasing clinical and research focus on cardiovascular diseases in AF patients with mental disorders, the stroke risk in patients with mental disorders is largely unknown. Prior studies have shown that AF patients with mental disorders are less likely to start oral anticoagulant therapy (OAT) than those without,[9,10] and that those who receive OAT have worse anticoagulation control[9,11,12] and increased risk of major haemorrhage.[11,13] However, these studies only assessed outcomes in patients receiving OAT for at least 100-180 days, excluding patients who never initiated therapy and those who discontinued therapy shortly after initiation.[11,13]

We aimed to examine the prognostic importance of severe mental disorders in AF patients. In a nationwide cohort of patients with incident AF, we conceived a matched cohort study to compare the risk of stroke, fatal thromboembolic events, and major bleeding in AF patients with a prior diagnosis of schizophrenia, severe depression, or bipolar disease to matched comparison cohorts without these disorders. By sequentially adjusting for stroke risk factors, bleeding risk factors, comorbidity, and use of OAT, we sought to further characterize the association between mental disorders and AF outcomes.

METHODS

Data sources

This cohort study linked three well-established Danish registries nationwide; the National Patient Register[14], the National Prescription Register[15], and the Civil Registration System.[16] The National Patient Register holds information on dates of admission and discharge, and discharge diagnoses classified according to the *International Classification of Diseases* (ICD) for more than 99% of hospital admissions in Denmark. The Prescription Registry contains data on all prescription purchases by Danish residents since 1995. Data includes the patients' civil registration number, date of dispensing, and type and quantity of drug prescribed. The Danish Person Registry holds data on sex, date of birth, vital and emigration status. Supplementary Table 1 provides information on codes for all diagnoses and medications. The registries were linked using the unique personal civil registration number assigned to all Danish residents, allowing a true population-based study covering all 5,6 million inhabitants of Denmark during the study period. We performed all linkages within Statistics Denmark, a governmental institution that collects and processes information for statistical and scientific purposes.[17] The study was approved by the Danish Data Protection Agency (Record number 2012-41-0633). According to Danish law, approval from an ethics committee is not required for anonymous registry-based studies.

Study population

We established a cohort of all patients with incident non-valvular AF, defining non-valvular AF as presence of AF, and baseline absence of mitral stenosis or mechanical heart valves. Specifically, we identified all patients discharged with a first hospital diagnosis of non-valvular AF between 2000 and 2015. To ensure sufficient clinical record history for treatment and diagnoses, we excluded patients who had not been residents in Denmark for at least 1 year before date of AF diagnosis

(index date). We further excluded patients with valvular AF; patients who died on the day of AF diagnosis; and patients with a fatal thromboembolic event defined as death within the following 30 days of ischemic stroke, systemic embolism, pulmonary embolism or myocardial infarction before AF diagnosis (Supplementary Figure 1). The positive predictive value (PPV) of an AF diagnosis in the National Patient Register is 95% (95% CI 89-98).[18]

Exposure

Through the National Patient Register, we identified all patients in the study population with an inpatient or outpatient diagnosis of schizophrenia, bipolar disease or severe depression before the index date. In Denmark, these mental disorders are primarily treated in public hospitals ensuring a high coverage of contacts with psychiatric disorders. The PPV of a diagnosis of mental disorders in the National Patient Register is 98% (95% CI 90-99).[18]

To control for confounding by reducing imbalance in the data and thereby model dependence and bias, we used Coarsened Exact Matching to produce a one-to-five match of patients with schizophrenia, severe depression, or bipolar disease on age, sex and calendar time (year of index date) to comparison cohorts of AF patients without mental disorders.[19] Patients age was grouped in approximately 5-year intervals based on the statistical software package Stata's (Stata Corp, version 14) function *cem*'s algorithm for automatic coarsening.[20] To evaluate the effect of matching on the balance between baseline variables we estimated the absolute standardized differences before and after matching.

Patient characteristics

Baseline comorbidity was defined according to medication claims within the year before the AF diagnosis and/or history of primary or secondary hospital discharge diagnoses (excluding emergency room diagnoses) since 1994. Comorbidity information included cardiovascular and metabolic diseases, and lifestyle related diseases (e.g. alcohol-related diseases such as alcoholic liver disease, and alcoholic polyneuropathy, cardiomyopathy, gastritis or myopathy, and alcohol-induced pancreatitis). We further combined baseline information into the CHA_2DS_2VASc stroke risk score[21] to summarize perceived stroke risk at baseline, and the HAS-BLED score[22] as a measure of bleeding risk at baseline (see score definitions in Supplementary Table 2).

Outcomes

Study outcomes were ischemic stroke, fatal thromboembolic events of ischemic stroke, systemic embolism, pulmonary embolism or myocardial infarction (as defined above), and major bleeding events recorded as intracranial, gastro-intestinal, and major bleeding in various anatomical positions and reported in total as 'any bleeding'. We derived all outcomes from hospital diagnoses in the National Patient Register. Stroke diagnoses were required to be primary in-hospital codes, excluding emergency room and ambulatory diagnoses, to ensure higher validity.

Statistical analyses

We followed all patients from their AF diagnosis and up to five years after baseline. Follow-up was censored at time of death, migration, study end (November 21, 2016), or the outcome of interest, whichever came first. Patient baseline characteristics were presented as proportions for discrete variables and means with standard deviations (SD) for continuous variables. Crude incidence rates were calculated as number of events divided by person-time. Cumulative incidence functions (by

means of the Aalen-Johansen estimator), assuming death as competing risk, were used to depict risk of outcome during follow-up. We assessed the association between each mental disorder and study outcome using Cox Proportional hazard regression with stratification on the matched groups. To assess to which extent the observed association could be explained by comorbidity and/or use of OAT, we performed sequential cumulative adjustment for 1) stroke risk and bleeding risk as summarized by components of the CHA_2DS_2VASc and HAS-BLED scores, and comorbidities not included in CHA_2DS_2VASc and HAS-BLED (chronic pulmonary disease, cancer, and venous thromboembolism), and 2) use of OAT during follow-up modelled as a time-varying covariate shifting from untreated to treated status at first observed prescription of any OAC. We excluded age and sex in the CHA_2DS_2VASc and HAS-BLED scores as these were included as matching factors and perfectly balanced between comparison cohorts (Supplementary Table 3). The distribution of time to OAC treatment initiation was presented by cumulative incidence curves (Supplementary Figure 2). Point estimates were reported with 95% confidence intervals (CI) and a p-value less than 0.05 was considered statistically significant.

RESULTS

We identified 260,974 AF patients during the study period. After exclusions, the study cohort comprised 253,741 AF patients of which 534 patients had schizophrenia, 400 had severe depression, and 569 had bipolar disease (Supplementary Figure 1). Table 1 shows baseline characteristics according to presence and type of mental disorder. AF patients with schizophrenia were substantially younger (mean age 64.5 years) whereas the age of patients with severe depression (73.7 years) and bipolar disease (73.0 years) was comparable with patients without mental disorders (73.3 years). Baseline stroke risk appeared lower in patients with schizophrenia; the mean CHA_2DS_2-VASc score was 2.5 versus 3.1 in patients without mental disorders. However, this was explained by the lower age of schizophrenic patients. The CHA_2DS_2-VASc score was 3.6 in patients with severe depression and 3.3 in patients with bipolar disease (Table 1). The higher CHA_2DS_2-VASc score in patients with severe depression was primarily driven by a large proportion of females (61.8% vs. 46.7% in comparisons) and patients with prior stroke (30.3% vs. 16.9%). In comparison, 14.2% of schizophrenic patients had prior stroke; they also had lower prevalence of hypertension, myocardial infarction, and peripheral arterial disease. Compared with patients with no mental disorder, the HAS-BLED score was also higher in patients with severe depression and bipolar disease whereas it was lower in patients with schizophrenia. Alcohol-related diseases were prevalent across all mental disorders, particularly for patients with schizophrenia or bipolar disease (~20% vs. 4% in comparisons). Supplemental Table 3 shows characteristics for patients with schizophrenia, severe depression, and bipolar disease and their matched comparisons. After matching, the mean CHA_2DS_2-VASc score was 2.3 in AF patients without schizophrenia (Supplementary Table 3).

Ischemic stroke

Figure 1 displays cumulative incidence curves for ischemic stroke in the matched cohorts. Rates of ischemic stroke at 5 years was 1.96 events per 100 person-years in schizophrenic AF patients vs. 1.30 in matched comparisons (Table 2), yielding a crude HR of 1.37 (95% CI 0.88-2.14) with confidence intervals including unity (Figure 2). After adjustment for stroke risk as summarized by the CHA_2DS_2-VASc and HAS-BLED scores and other comorbidities, this HR was 1.29 (95% CI 0.81-2.07) (Figure 2). Rates of OAT initiation in AF patients with mental disorders was substantially lower than in matched comparisons (Supplementary Figure 2), and after additional adjustment for OAT use during follow-up the HR of ischemic stroke was 1.16 (95% CI 0.72-1.87) (Figure 2). At 5-years the rate of ischemic stroke was 2.74 per 100 person-years in patients with severe depression vs. 1.93 in matched comparisons (crude HR of 1.36, 95% CI 0.89-2.08). Similar to patients with schizophrenia, the crude HR was substantially attenuated by sequential adjustment for stroke risk factors, comorbidity, and OAT (HR 1.01, 95% CI 0.64-1.58) (Figure 2). This pattern of diminishing HRs with sequential adjustment for stroke risk factors and OAT was also evident in patients with bipolar disease in whom the crude HR was 1.04 (95% CI 0.69-1.56) and the fully adjusted HR was 0.85 (95% CI 0.55-1.29). Thus, compared with AF patients without mental disorders, the fully adjusted HRs indicated comparable HRs of ischemic stroke across all mental disorders with wide CIs that crossed unity (Figure 2).

Fatal thromboembolic events

During 5-years follow-up, 19 fatal thromboembolic events occurred in AF patients with schizophrenia, 11 in patients with severe depression, and 20 in patients with bipolar disease. Accordingly, rates of fatal thromboembolic events per 100 person-years was substantially lower than rates of ischemic stroke; 1.43 for schizophrenia vs. 0.52 in matched comparisons, 1.03 vs. 0.82

for severe depression, and 1.41 vs. 0.83 for patients with bipolar disease (Table 2). Notwithstanding, due to the low rate in the matched comparisons, cumulative incidence curves revealed distinct differences in rates of fatal thromboembolic events in patients with schizophrenia vs. matched comparisons (Figure 3) and to lesser extent in patients with bipolar disease. The equivalent 5-year HR was 3.16 (95% CI 1.78-5.61) decreasing to 2.88 (95% CI 1.57-5.28) after adjustment for stroke risk factors, comorbidity, and OAT (Figure 2). The unadjusted HR of fatal thromboembolic events in patients with severe depression vs. matched comparisons was 1.31 (95% CI 0.67-2.56). After adjustment for stroke risk factors, comorbidity, and OAT, the HR was 0.75 (95% CI 0.37-1.52). In patients with bipolar disease the crude HR was 1.53 (95% CI 0.93-2.53) compared with matched comparisons. Following sequential adjustment the HR was 1.23 (95% CI 0.72-2.09) (Figure 2).

Major bleeding

The cumulative incidence curves showed higher rates of major bleeding in patients with schizophrenia and severe depression compared with their matched comparisons, whereas the curves for patients with bipolar disease overlapped with the comparisons (Figure 4). At 5 years, the rate of bleeding was 3.72 events per 100 person-years in schizophrenic patients vs. 2.62 in matched comparisons (crude HR of 1.37, 95% CI 0.99-1.90), 4.06 per 100 person-years in patients with severe depression vs. 3.24 in matched comparisons (crude HR of 1.25, 95% CI 0.87-1.78), and 2.90 vs. 3.27 in patients with bipolar disease (HR of 0.82, 95% CI 0.58-1.15) (Table 2, Figure 2). Sequential adjustment for the components of the CHA_2DS_2-VASc and HAS-BLED scores (including use of aspirin, NSAID and clopidogrel at baseline) and use of OAT attenuated the association in patients with schizophrenia and severe depression (Figure 2).

DISCUSSION

Principal findings

This nationwide cohort study revealed a low prevalence of severe mental disorders among patients with incident AF in Denmark. Patients with schizophrenia or severe depression experienced higher risk of ischemic stroke and major bleeding compared with matched AF patients without mental disorders, although the differences were not statistically significant. However, after sequential adjustment for stroke and bleeding risk factors, comorbidity, and use of OAT, hazard rates were comparable with matched comparisons, suggesting that the excess risk in patients with schizophrenia and severe depression derived from higher prevalence of risk factors for stroke and bleeding and differences in use of OAT. In comparison, bipolar disease was not associated with higher risk of stroke and bleeding both before and after adjustment. Few thromboembolic events occurred during follow-up. Nonetheless, we noted a substantially higher mortality after a thromboembolic event in patients with schizophrenia than in matched comparisons.

Strengths and limitations

These estimates of stroke risk and thromboembolic events in AF patients are based on a nationwide cohort study conducted in a setting where virtually all medical care is provided free of charge, and with complete follow-up through nationwide registries. Nonetheless, despite universal tax-supported health care in Denmark, diagnoses in patients with mental disorders may have been underreported.[23,24] From the current study, we are not able to conclude whether the low prevalence of AF patients with mental disorders reflect the true picture or whether AF may be under-diagnosed in these patients. Likewise, we cannot exclude a possibility for differential misclassification of study outcomes, if stroke and thromboembolic events were under-diagnosed in patients with severe mental disorders. Such misclassification would bias our estimates toward the null. Furthermore, we included only patients with mental disorders recorded in the hospital register, and the prevalence is

likely underestimated, mainly with regard to severe depression. However, we infer that the majority of patients with schizophrenia and bipolar disease are in contact with the psychiatric hospital system due the severity of these conditions. It is also important to note that we only had information on psychiatric admissions from 1995 onwards. Thus, patients with a diagnosis before 1995 and no recorded diagnosis thereafter would not be included in the exposed cohort. Lack of data on alcohol, smoking, exercise, and other lifestyle related risk factors associated with increased risk of study outcomes is another limitation. We were able to adjust for hospital diagnoses of alcohol-related conditions and many other lifestyle-related diseases including chronic pulmonary disease, diabetes, liver disease, cardiovascular disease, and cancer, which were more prevalent among patients with mental disorders. Nonetheless, incomplete control for these factors likely lead to residual confounding, e.g. bleeding risk due to alcohol abuse.[25,26] Likewise, we did not assess the association between anti-psychotic medications and stroke risk in this study. Finally, use of OAT was determined based on prescription redemption, which may be a limitation, as some patients may not take their medications. Our data did not contain information on the quality and compliance with OAT, which may be lower among patients with mental disorders due to cognitive limitations and maladaptive behaviours.[27]

Comparison with other studies

Our findings are concordant with two prior studies on outcomes of AF patients with mental disorders receiving warfarin.[11,13] In a US cohort study of 9,345 Medicaid recipients receiving two or more warfarin prescriptions less than 100 days apart, Schauer et al.[13] demonstrated HRs of 1.36 (95% CI 1.06-1.74) for ischemic stroke in patients with mental disorders compared with patients without. In another US cohort study, Paradise et al.[11] showed that mental disorders was associated with an increased risk of major bleeding (HR of 1.19, 95% CI 1.11-1.27) in patients with any

mental disorder vs. propensity matched comparisons in 103,897 patients receiving warfarin for at least 6 months through the Veterans Health Administration. Both studies only included patients who were considered appropriate for OAT and who actually received it and remained successfully on treatment for an extended period. Thus, these results may not reflect stroke risk in all patients with mental disorders.

Our findings expand prior studies by including all AF patients regardless of OAT use. We saw a noticeable lower rate of OAT initiation in patients with mental disorders compared with matched comparisons, which is in line with prior studies showing that AF patients with mental disorders are less likely to receive OAT.[9,10] Schmitt et al.[10] found that AF patients with mental disorders had a higher prevalence of stroke risk factors and contraindications to OAT. Thus, lower treatment rates in patients with mental disorders may reflect appropriate attention to bleeding risk. On the other hand, when restricting to patients eligible for OAT, patients with mental disorders remained less likely to receive OAT.[10] As the higher stroke rates in our study appeared to be due to differences in stroke risk factors, comorbidity, and receipt of OAT, any disparities in the care of AF patients with mental disorders requires close attention. Other studies have shown that patients with mental disorders have worse OAT control.[9,11,12] Walker et al.[9] found that when prescribed warfarin, AF patients with mental disorders were substantially more likely to have highly supra-therapeutic International Normalized Ratio (INR) values than those without mental disorders (27.3% vs. 1.6% had at least one INR measurement above 5.0). However, this assessment was based on a sub-cohort of only 84 AF patients and should be interpreted with caution.

The higher mortality within the 30 days following a thromboembolic event in patients with schizophrenia is a concern and emphasizes the need for vigilant follow-up in this patient population.

The finding is in line with prior studies reporting increased cardiac mortality in patients with schizophrenia.[24,28] Future studies are encouraged to explore potential reasons, which are likely multifactorial and may entail both severity of illness, comorbidity, quality of care, and factors beyond patient care.[29]

Conclusions

In conclusion, this study showed that AF patients with schizophrenia or severe depression were at increased risk of ischemic stroke and major bleeding. However, the fully adjusted hazard rates were comparable with matched comparisons, indicating that the excess risk is due to a higher prevalence of risk factors for stroke and bleeding and lower use of OAT in patients with mental disorders. In comparison, rates were not increased in patients with bipolar disease. Patients with schizophrenia further experienced higher mortality following a thromboembolic event than matched comparisons. These findings highlight the importance of close attention to stroke and bleeding risk factors and potential disparities in receipt of OAT in AF patients with mental disorders. Our findings also identify challenges in the management of AF patients with mental disorders; the excess burden of stroke risk factors signifies the need for stroke prevention whereas the higher rates of major bleeding emphasize that cautious assessment of bleeding risk and quality of OAT may be particularly pertinent in these patients. In this respect, our findings indicate a need for optimized coordination and collaboration between general somatic and mental health services .

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Author Contributions

MS, FS and JNK had full access to all of the data in this study and take responsibility for the integrity of the data and the accuracy of the data analysis. SR, SPH and TBL provided the idea for the study. MS, FS, TBL, SPH, and SR defined the study concept and performed the critical interpretation of the data. MS drafted the article. All authors contributed critical revisions and approved the final version to be published.

Conflicts of Interest Disclosures

Associate Professor Larsen has served as an investigator for Janssen Scientific Affairs, LLC and Boehringer Ingelheim and has served as a speaker for Bayer, BMS/Pfizer, Boehringer Ingelheim. Senior Statistician Flemming Skjøth has served as a consultant for Bayer. Other authors – none declared.

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Ethics approval: The study was approved by the Danish Data Protection Agency (Record number 2012-41-0633).

Data sharing statement: No additional data are available

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FIGURE LEGENDS

Figure 1. Cumulative incidence of ischemic stroke in patients with atrial fibrillation and mental disorders and matched atrial fibrillation patients without mental disorders.

Figure 2. Crude and adjusted hazard ratios (HR) with 95% confidence intervals (CI) for ischemic stroke, fatal thromboembolic events, and major bleeding in atrial fibrillation patients with severe mental disorders compared with matched atrial fibrillation patients without mental disorders.

Figure 3. Cumulative incidence of fatal thromboembolic events in patients with atrial fibrillation and mental disorders and matched atrial fibrillation patients without mental disorder.

Figure 4. Cumulative incidence of major bleeding in patients with atrial fibrillation and mental disorders and matched atrial fibrillation patients without mental disorder.

Table 1. Descriptive characteristics of patients with incident atrial fibrillation in Denmark according to presence of mental health disorders before matching.

Characteristic, % (N)	No mental disorder (N=252,238)	Schizophrenia (N=534)	Severe depression (N=400)	Bipolar disease (N=569)
Demographic characteristics				
Females	46.7 (117,876)	45.7 (244)	61.8 (247)	59.6 (339)
Mean age (SD)	73.3 (13.1)	64.5 (13.7)	73.7 (14.0)	73.0 (11.2)
Stroke risk factors and comorbidity				
Mean CHA_2DS_2VASc score (SD)	3.1 (1.8)	2.5 (1.7)	3.6 (2.0)	3.3 (1.8)
Mean HASBLED score (SD)	2.2 (1.2)	1.9 (1.3)	2.5 (1.4)	2.5 (1.3)
Prior stroke	16.9 (42,585)	14.2 (76)	30.3 (121)	20.2 (115)
Heart failure	25.7 (64704)	30.0 (160)	30.3 (121)	29.3 (167)
Hypertension	42.6 (107,332)	26.6 (142)	44.5 (178)	36.6 (208)
Myocardial infarction	10.3 (26,089)	8.2 (44)	11.3 (45)	9.3 (53)
Peripheral arterial disease	7.6 (19,266)	6.7 (36)	10.0 (40)	9.0 (51)
Diabetes	12.9 (32,606)	24.3 (130)	15.8 (63)	20.2 (115)
Prior bleeding	26.4 (66,694)	28.1 (150)	44.0 (176)	37.6 (214)
Renal dysfunction	5.2 (13,003)	10.1 (54)	8.5 (34)	15.8 (90)
Prior venous thromboembolism	4.8 (12,081)	7.3 (39)	10.8 (43)	10.0 (57)
Chronic pulmonary disease	14.5 (36,615)	28.7 (153)	22.3 (89)	30.8 (175)
Cancer	15.9 (40,171)	12.9 (69)	14.8 (59)	17.0 (97)
Alcohol-related disease	4.2 (10,471)	19.1 (102)	11.0 (44)	20.9 (119)
Medication use within 365 days before index date				
Coumarin	14.4 (36,326)	5.1 (27)	8.8 (35)	12.1 (69)
NOAC	2.5 (6,347)	3.4 (18)	2.3 (9)	2.3 (13)
Aspirin	37.6 (94,951)	33.0 (176)	40.5 (162)	38.1 (217)
Clopidogrel	4.3 (10,936)	5.6 (30)	9.0 (36)	5.6 (32)
NSAID	26.7 (67,468)	25.1 (134)	27.3 (109)	25.0 (142)

Digoxin	12.4 (31,200)	9.9 (53)	8.8 (35)	12.1 (69)
Non-loop diuretics	36.2 (91,336)	25.1 (134)	38.8 (155)	34.4 (196)
Loop-diuretics	25.5 (64,337)	34.8 (186)	28.8 (115)	36.0 (205)
Beta-blocker	32.2 (81,335)	22.7 (121)	28.0 (112)	24.3 (138)
Calcium channel blocker	25.5 (64,355)	17.0 (91)	31.0 (124)	25.1 (143)
Renin-angiotensin inhibitor	35.5 (89,621)	23.8 (127)	37.5 (150)	32.0 (182)
Statins	24.6 (62,166)	23.2 (124)	26.0 (104)	27.4 (156)
Antiepileptics	4.0 (10,077)	24.3 (130)	16.0 (64)	39.5 (225)
Anticholinergics	0.2 (456)	27.2 (145)	2.3 (9)	5.3 (30)
Antipsychotics, lithium and anxiolytics/hypnotics	27.1 (68,302)	87.1 (465)	63.2 (253)	83.3 (474)
Antidepressants	14.5 (36,516)	34.8 (186)	78.5 (314)	61.0 (347)

Abbreviations:
SD: Standard deviation
NOAC: Non-vitamin K oral anticoagulant
NSAID: Non-steroidal anti-inflammatory drugs

Table 2. Number of events and rates of stroke, fatal thromboembolic events, and major bleeding at 5 years following incident atrial fibrillation.

	Patients	Ischemic stroke		Fatal thromboembolic events		Major bleeding	
Characteristic	N	Events, N	Rate	Events, N	Rate	Events, N	Rate
Entire unmatched AF comparison cohort	252,238	15,710	2.03	8,039	1.00	26,711	3.53
Schizophrenia							
Schizophrenia	534	25	1.96	19	1.43	46	3.72
Matched comparison cohort	2,669	114	1.30	47	0.52	225	2.62
Severe depression							
Severe depression	400	28	2.74	11	1.03	41	4.06
Matched comparison cohort	2,000	113	1.93	50	0.82	188	3.24
Bipolar disease							
Bipolar disease	569	28	1.90	20	1.41	39	2.90
Matched comparison cohort	2,845	164	2.04	74	0.83	274	3.27

Rates are calculated as number of events divided by person-time per 100 years.

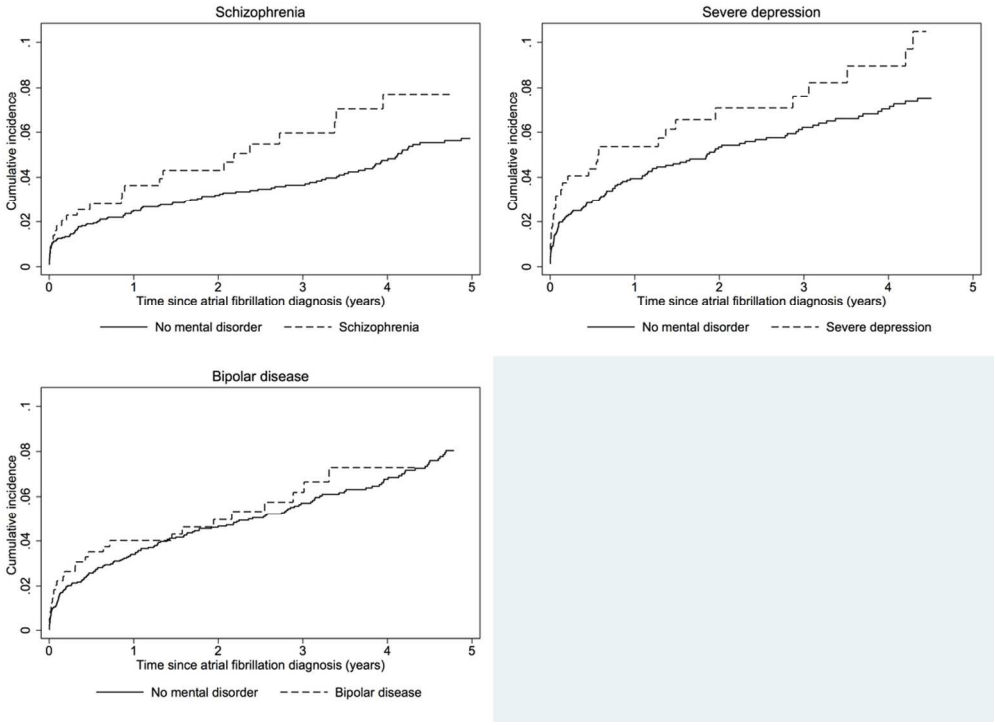

Figure 1

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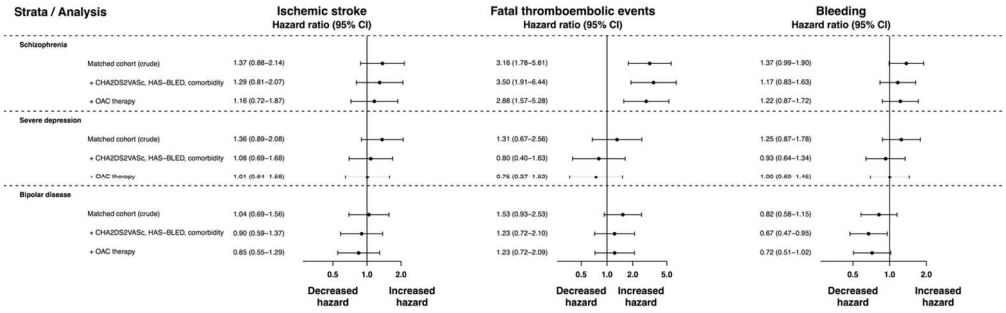

Figure 2

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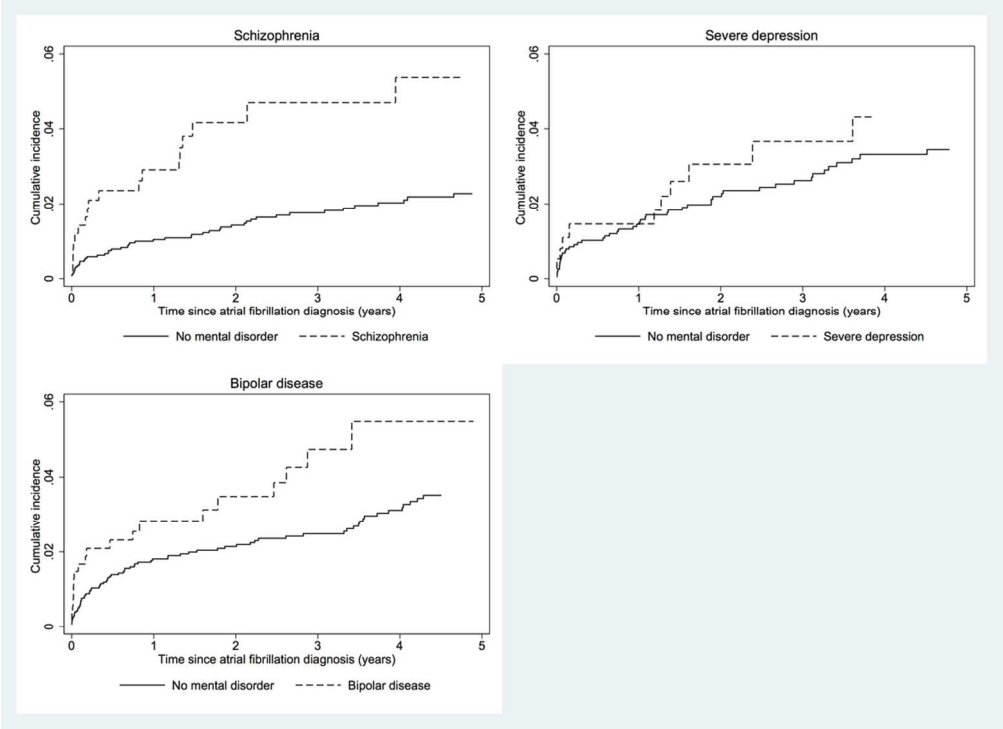

Figure 3

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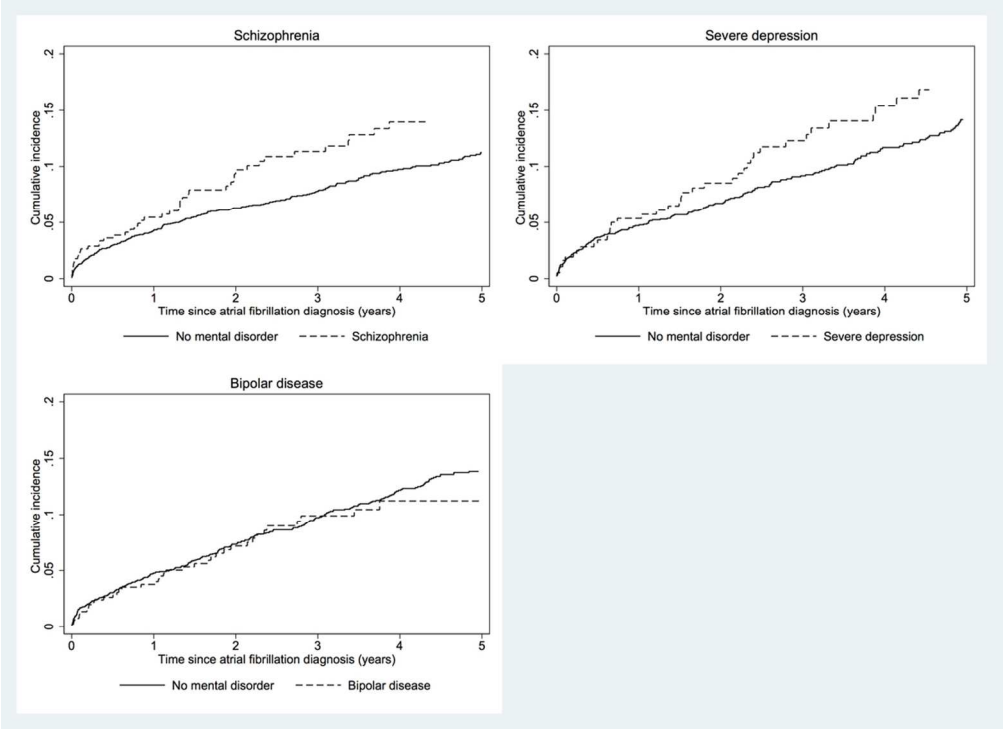

Figure 4

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SUPPLEMENTAL INFORMATION

Atrial fibrillation in patients with severe mental disorders and the risk of stroke, fatal thromboembolic events, and bleeding: a nationwide cohort study

Mette Søgaard,PhD[1,2], Flemming Skjøth, PhD[2,3], Jette Nordstrom Kjældgaard[1,2], BSCEE, Torben Bjerregaard Larsen, PhD[1,2,5], Søren Pihlkjær Hjortshøj, PhD[4,5], Sam Riahi, PhD[1,4,5]

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Supplementary tables and figures

Supplementary Table 1. Definitions on comorbidity, concomitant medication, and study outcomes according to ICD-10 codes and ATC-codes.

Diagnoses	International Classification of Diseases 10th revision (ICD-10) code	Anatomical Therapeutic Chemical (ATC) code
Study population		
Atrial fibrillation	I48	
Exposure		
Schizophrenia	F20	
Bipolar disease	F30 F31	
Severe depression	F322 F323 F332 F333	
Outcomes		
Ischemic stroke	I63 I64	
Major bleeding	I60 I61 I62 K250 K252 K254 K260 K262 K264 K270 K272 K274 K280 K282 K290 K920 K921 K922 D62 J942 H113 H356 H431 N02 R04 R31 R58	
Thromboembolic events		
Ischemic stroke	I63 I64	
Systemic embolism	I74	
Pulmonary embolism	I26	
Myocardial infarction	I21 I23	
Baseline covariates		
Heart failure	I110 I130 I132 I420 I50	
Hypertension		See specified definition[a]
Peripheral vascular/ischemic disease	I702 I703 I704 I705 I706 I707 I708 I709 I71 I739	
Diabetes	E100 E101 E109 E110 E111 E119	A10
Prior bleeding	K250 K252 K254 K260 K262 K264 K270 K272 K274 K280	

	K282 K290 K920 K921 K922 D62 J942 H113 H356 H431 N02 R04 R31 R58	
Renal dysfunction	I12 I13 N00 N01 N02 N03 N04 N05 N07 N11 N14 N17 N18 N19 Q61	
Prior VTE	I801 I802 I803 I808 I809 I819 I636 I676 I822 I823 I828 I829	
Chronic pulmonary disease	J40 J41 J42 J43 J44 J45 J46 J47 J60 J61 J62 J63 J64 J65 J67 J684 J701 J703 J841 J920 J961 J982 J983	
Cancer	C	
Alcohol-related disease	E224 E529A F10 G312 G621 G721 I426 K292 K70 K860 L278A O354 T51 Z714 Z721	
Medications within 365 days before index date		
Coumarin		B01AA
NOAC		B01AF01 B01AF02 B01AE07
Aspirin		B01AC06
Clopidogrel		B01AC04
NSAID		M01A
Digoxin		C01AA05
Non-loop diuretics		C02DA C02L C03A C03B C03D C03E C03X C07C C07D C08G C09BA C09DA C09XA52
Loop-diuretics		C03C
Beta-blocker		C07
Calcium channel blocker		C07F C08 C09BB C09DB
Renin-angiotensin inhibitor		C09
Statins		C10

Abbreviations: VTE, venous thromboembolism; NOAC, Non-vitamin K oral anticoagulant; NSAID, Non-steroidal anti-inflammatory drugs.

[a]We identified subjects with hypertension from combination treatment with at least two of the following classes of antihypertensive drugs:

I· Alpha adrenergic blockers (C02A, C02B, C02C)

II· Non-loop diuretics (C02DA, C02L, C03A, C03B, C03D, C03E, C03X, C07C, C07D, C08G, C09BA, C09DA, C09XA52)

III· Vasodilators (C02DB, C02DD, C02DG, C04, C05)

IV· Beta blockers (C07)

V· Calcium channel blockers (C07F, C08, C09BB, C09DB)

VI· Renin-angiotensin system inhibitors (C09)

Supplementary Table 2. Risk score definitions.

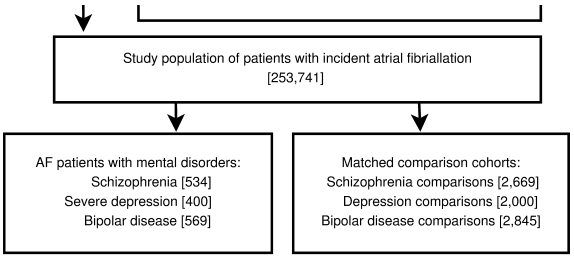
Risk score	Points if present
CHA_2DS_2VASc[a]	
Congestive heart failure or Left Ventricular Dysfunction	1
Hypertension	1
Age ≥ 65 years	1
Age ≥ 75 years	1
Diabetes mellitus	1
Stroke (ischemic stroke, transient ischemic disease or systemic embolism)	2
Vascular disease (myocardial infarction, peripheral arterial disease, or aortic plaque)	1
Sex category (female)	1
HAS-BLED[b]	
Hypertension	1
Abnormal renal function	1
Abnormal hepatic function	1
Stroke (ischemic stroke or transient ischemic attack)	1
Bleeding	1
Labile international normalized ratio[c]	1
Elderly age (≥ 65 years)	1
Drugs (aspirin, clopidogrel, or non-steroidal anti-inflammatory drugs)	1
Alcohol intake	1

[a]Reflects stroke risk in atrial fibrillation patients not in anticoagulant therapy (Lip GYH, Nieuwlaat R, Pisters R, Lane DA, Crijns HJGM. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. Chest 2010;137(2):263-72)

[b]Reflects bleeding risk in atrial fibrillation patients undergoing anticoagulant therapy (Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJGM, Lip GYH. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. Chest 2010;138(5):1093-100).

[c]Not included due to unavailable information

Supplementary Figure 1. Flowchart of the study population.



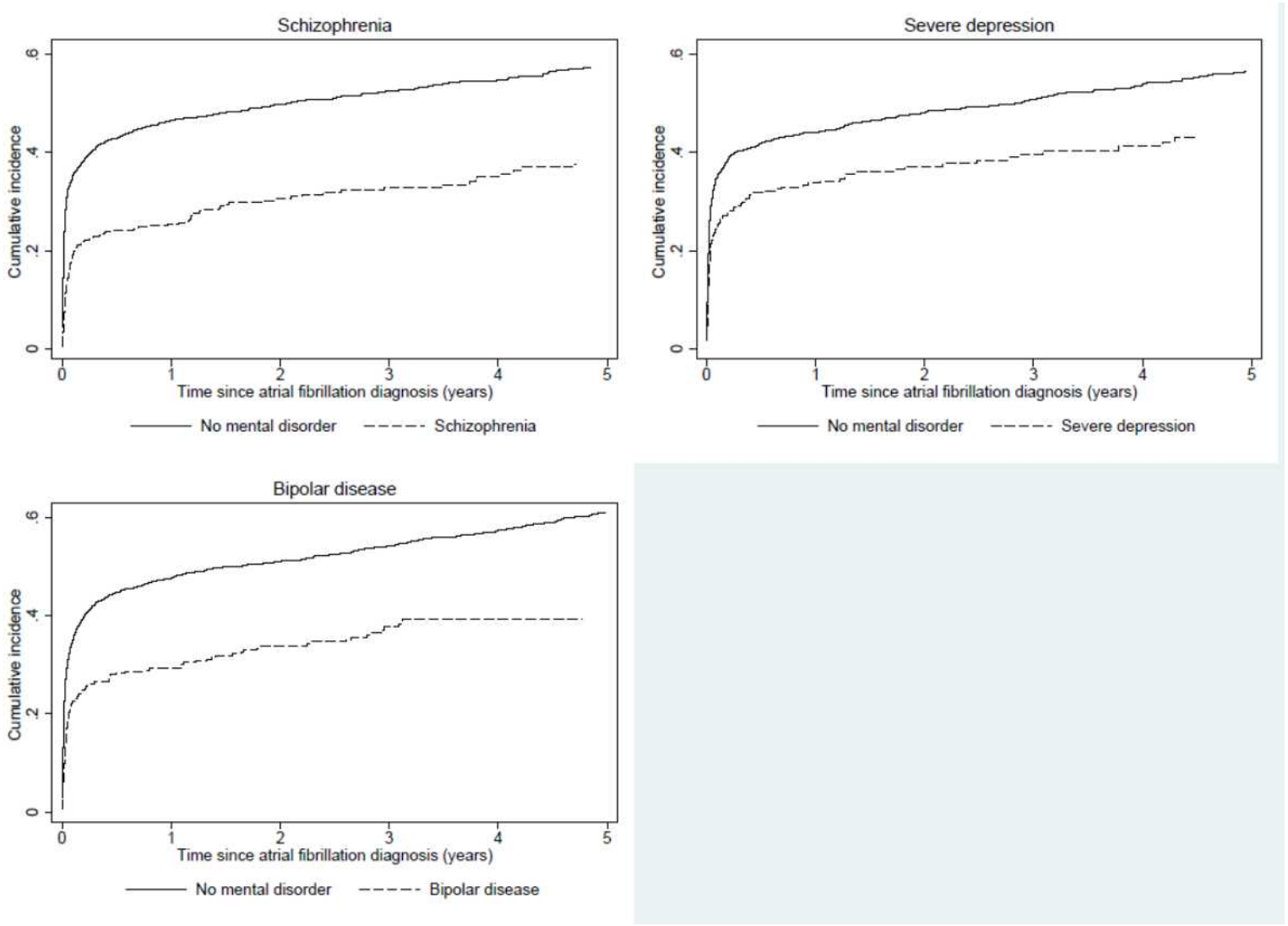
Supplementary Table 3. Descriptive characteristics of AF patients with schizophrenia, severe depression, or bipolar disease and their matched comparison cohorts.

Characteristic, % (N)	Schizophrenia		Severe depression		Bipolar disease	
	Matched AF comparisons	Schizophrenia	Matched AF comparisons	Severe depression	Matched AF comparisons	Bipolar disease
Total number	2,669	534	2,000	400	2,845	569
Females	45.7 (1,219)	45.7 (244)	61.8 (1,235)	61.8 (247)	59.6 (1,695)	59.6 (339)
Mean age (SD)	64.5 (13.7)	64.5 (13.7)	73.5 (14.0)	73.7 (14.0)	73.1 (11.2)	73.0 (11.2)
Mean CHA_2DS_2VASc score (SD)	2.3 (1.8)	2.5 (1.7)	3.3 (1.8)	3.6 (2.0)	3.2 (1.8)	3.3 (1.8)
Mean HASBLED score (SD)	1.8 (1.3)	1.9 (1.3)	2.2 (1.2)	2.5 (1.4)	2.2 (1.2)	2.5 (1.3)
Prior stroke	13.3 (355)	14.2 (76)	17.9 (358)	30.3 (121)	17.8 (505)	20.2 (115)
Heart failure	19.4 (518)	30.0 (160)	23.4 (469)	30.3 (121)	25.3 (720)	29.3 (167)
Hypertension	38.6 (1030)	26.6 (142)	44.1 (882)	44.5 (178)	45.2 (1287)	36.6 (208)
Myocardial infarction	6.9 (185)	8.2 (44)	10.7 (213)	11.3 (45)	9.6 (273)	9.3 (53)
Peripheral arterial disease	5.7 (152)	6.7 (36)	8.1 (161)	10.0 (40)	7.1 (201)	9.0 (51)
Diabetes	12.9 (344)	24.3 (130)	12.9 (259)	15.8 (63)	12.6 (358)	20.2 (115)
Prior bleeding	13.0 (346)	28.1 (150)	15.4 (307)	24.0 (96)	14.4 (409)	23.0 (131)
Renal dysfunction	4.8 (127)	10.1 (54)	4.1 (82)	8.5 (34)	5.1 (144)	15.8 (90)
Prior venous thromboembolism	4.8 (128)	7.3 (39)	5.9 (119)	10.8 (43)	4.7 (135)	10.0 (57)
Chronic pulmonary disease	13.3 (355)	28.7 (153)	14.9 (299)	22.3 (89)	16.1 (458)	30.8 (175)
Cancer	12.9 (345)	12.9 (69)	17.9 (357)	14.8 (59)	17.3 (493)	17.0 (97)
Alcohol-related disease	5.9 (158)	19.1 (102)	3.6 (73)	11.0 (44)	4.3 (122)	20.9 (119)

Coumarin	13.3 (356)	5.1 (27)	13.7 (273)	8.8 (35)	14.3 (407)	12.1 (69)
NOAC	3.7 (99)	3.4 (18)	2.8 (56)	2.3 (9)	3.4 (98)	2.3 (13)
Aspirin	29.6 (790)	33.0 (176)	37.2 (744)	40.5 (162)	37.7 (1073)	38.1 (217)
Clopidogrel	4.3 (116)	5.6 (30)	5.3 (106)	9.0 (36)	5.0 (143)	5.6 (32)
NSAID	27.1 (722)	25.1 (134)	27.1 (542)	27.3 (109)	26.2 (745)	25.0 (142)
Digoxin	6.8 (182)	9.9 (53)	9.3 (187)	8.8 (35)	10.7 (304)	12.1 (69)
Non-loop diuretics	31.4 (839)	25.1 (134)	38.2 (764)	38.8 (155)	38.3 (1089)	34.4 (196)
Loop-diuretics	18.7 (500)	34.8 (186)	24.4 (488)	28.8 (115)	23.7 (675)	36.0 (205)
Beta-blocker	31.4 (837)	22.7 (121)	33.8 (676)	28.0 (112)	34.4 (980)	24.3 (138)
Calcium channel blocker	22.1 (591)	17.0 (91)	27.1 (543)	31.0 (124)	26.5 (753)	25.1 (143)
Renin-angiotensin inhibitor	34.2 (914)	23.8 (127)	37.0 (741)	37.5 (150)	39.2 (1115)	32.0 (182)
Statins	26.4 (704)	23.2 (124)	26.6 (531)	26.0 (104)	28.3 (804)	27.4 (156)
Antiepileptics	3.6 (95)	24.3 (130)	4.7 (94)	16.0 (64)	4.5 (129)	39.5 (225)
Anticholinergics	<4	<4	0.2 (4)	2.3 (9)	0.1 (4)	5.3 (30)
Antipsychotics, lithium and anxiolytics/hypnotics	21.4 (571)	87.1 (465)	26.6 (532)	63.2 (253)	28.8 (820)	83.3 (474)
Antidepressants	14.1 (375)	34.8 (186)	16.1 (323)	78.5 (314)	15.9 (453)	61.0 (347)

Abbreviations:
SD: Standard deviation
NOAC: Non-vitamin K oral anticoagulant
NSAID: Non-steroidal anti-inflammatory drugs

Supplementary Figure 2. Cumulative incidence curves of initiation of oral anticoagulation therapy in age, sex and calendar time matched atrial fibrillation patients with and without mental disorders.



STROBE (Strengthening The Reporting of OBservational Studies in Epidemiology) Checklist

A checklist of items that should be included in reports of observational studies. You must report the page number in your manuscript where you consider each of the items listed in this checklist. If you have not included this information, either revise your manuscript accordingly before submitting or note N/A.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Section and Item	Item No.	Recommendation	Reported on Page No.
Title and Abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/Rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study Design	4	Present key elements of study design early in the paper	1, 2, 5, 6-9
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-9
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6
		Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	N/A
		Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants	N/A
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed	7
		Case-control study—For matched studies, give matching criteria and the number of controls per case	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-9

Section and Item	Item No.	Recommendation	Reported on Page No.
Data Sources/ Measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-9
Bias	9	Describe any efforts to address potential sources of bias	7-9
Study Size	10	Explain how the study size was arrived at	6-7
Quantitative Variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-9
Statistical Methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8-9
		(*b*) Describe any methods used to examine subgroups and interactions	8-9
		(*c*) Explain how missing data were addressed	9
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	9 N/A N/A
		(*e*) Describe any sensitivity analyses	N/A
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10, Flowchart
		(b) Give reasons for non-participation at each stage	Flowchart
		(c) Consider use of a flow diagram	Figure 1 in sup
Descriptive Data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	23-24
		(b) Indicate number of participants with missing data for each variable of interest	N/A
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome Data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	Table 2
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	N/A
		Cross-sectional study—Report numbers of outcome events or summary measures	N/A

Section and Item	Item No.	Recommendation	Reported on Page No.
Main Results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Figure 2
		(*b*) Report category boundaries when continuous variables were categorized	10-12
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Table 2
Other Analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key Results	18	Summarise key results with reference to study objectives	13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-16
Generalisability	21	Discuss the generalisability (external validity) of the study results	13-16
Other Information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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