

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}

¹Department of Cardiology, Aalborg University Hospital, Denmark

²Aalborg Thrombosis Research Unit, Department of Clinical Medicine, Faculty of Health, Aalborg University, Aalborg, Denmark

³Unit for Clinical Biostatistics, Aalborg University Hospital, Denmark

⁴Department of Clinical Medicine, Aalborg University, Denmark

⁵AF-Study group, Aalborg University Hospital, Denmark

Supplementary tables and figures

Supplementary Table 1: Definitions on comorbidity, concomitant medications, and study outcomes 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, 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.

^aWe 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.

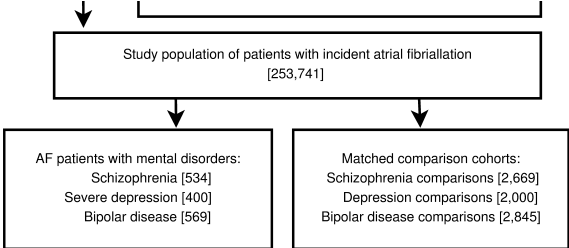
Risk score	Points if present
CHA₂DS₂VASc^a	
Congestive heart failure or Left Ventricular Dysfunction	1
Hypertension	1
Age ≥ 65 years	1
Age ≥ 75 years	1
Diabetes mellitus	1
Stroke (ischemic stroke, transient ischemic disease or systemic embolism)	2
Vascular disease (myocardial infarction, peripheral arterial 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

^aReflects 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)

^bReflects 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).

^cNot 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 ₂ DS ₂ VASc 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.

