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MENTAL HEALTH CONDITIONS IN PATIENTS WITH ATRIAL FIBRILLATION

Impact on treatment quality and prognosis

Konsta Teppo

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ABSTRACT

Background: Patients with mental health conditions (MHCs) face barriers in health care and often have undertreated comorbidities. The purpose of this dissertation was to evaluate the treatment and prognosis of patients with atrial fibrillation (AF) suffering from MHCs. **Methods**: The nationwide registry-based Finnish Anticoagulation in Atrial Fibrillation cohort covers all patients diagnosed with AF in Finland during 2004–2018 at any level of care. The use of oral anticoagulant (OAC) therapy and rhythm control therapies, as well as ischemic stroke, bleeding and mortality outcomes, were assessed in patients with and without depression, anxiety disorder, bipolar disorder, schizophrenia or any MHC. **Results**: In total, 239,222 patients diagnosed with incident AF in Finland between 2007 and 2018 were identified in this study, with a 19.9% prevalence of any MHC. Patients with any MHC were less likely to initiate OAC therapy than patients without MHCs (64.9% vs. 73.3%, $p < 0.001$). Patients with MHCs had similar adherence to non-vitamin K antagonist oral anticoagulants (NOACs) in the implementation phase of the therapy, but they discontinued NOAC therapy 16 % more often than patients without MHCs. Rhythm control therapies, including antiarrhythmic drugs, cardioversion and catheter ablation, were used less often for patients with MHCs compared to patients without MHCs. Crude rates of ischemic stroke, bleeding and mortality were all higher in patients with MHCs than in patients without MHCs. None of the MHC categories were independently associated with the risk of ischemic stroke, but any MHC, depression and schizophrenia were associated with higher mortality. Furthermore, any MHC, depression and anxiety disorders were associated with a higher risk of bleeding. The lower use of OAC therapy partly explained the higher crude mortality and ischemic stroke rates in patients with MHCs. **Conclusions**: Interventions are needed to improve stroke prevention in patients with AF and MHCs. Patients comorbid with MHCs have worse crude outcomes than patients without MHCs. MHCs are independently associated with higher mortality and bleeding risks but not with the risk of ischemic stroke in patients with AF.

KEYWORDS: Atrial fibrillation, mental health conditions, psychiatric disorders, oral anticoagulant therapy, medication adherence, rhythm control therapy, outcomes

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TIIVISTELMÄ

Tausta: Mielenterveyden häiriöitä sairastavien potilaiden somaattiset sairaudet ovat usein alihoidettuja. Tässä väitöskirjatyössä selvitetään mielenterveyden häiriöiden yhteyttä hoidon laatuun ja ennusteeseen eteisvärinäpotilailla. **Menetelmät**: Finnish Anticoagulation in Atrial Fibrillation -kohortti kattaa kaikki Suomen eteisvärinäpotilaat vuosilta 2004–2018. Tutkimuksessa tarkasteltiin antikoagulaatiohoidon (AK-hoidon) toteutumista, rytmikontrollihoitojen käyttöä sekä päätetapahtumien ilmaantuvuutta mielenterveyden häiriöitä sairastavilla potilailla. **Tulokset**: Tässä tutkimuksessa vuosien 2007 ja 2018 välillä uusi eteisvärinä todettiin yhteensä 239,222 potilaalla, joista 19,9 % sairasti jotain mielenterveyden häiriötä. Mielenterveyden häiriöitä sairastavat potilaat aloittivat muita harvemmin AK-hoidon (64,9 % vs. 73,3 %, $p<0,001$). Suoria antikoagulantteja käytettäessä mielenterveyden häiriötä sairastavat potilaat keskeyttivät hoidon 16 % muita useammin, mutta hoitoon sitoutuminen ei muutoin eronnut potilaiden välillä. Rytmihäiriön estolääkkeitä, rytminsiirtoa, sekä katetriablaatiota käytettiin harvemmin mielenterveyden häiriöitä sairastavilla potilailla kuin muilla. Mielenterveydenhäiriöitä sairastavilla oli suurempi vakioimaton aivoinfarktin, verenvuotojen, sekä kuoleman ilmaantuvuus. Mikään tutkituista mielenterveyden häiriöistä ei ollut itsenäisesti yhteydessä korkeampaan aivoinfarktin riskiin, mutta masennus, skitsofrenia sekä kaikkien mielenterveyden häiriöiden yhdistelmämuuttuja olivat yhteydessä korkeampaan kuolleisuuteen. Lisäksi masennus, ahdistuneisuushäiriö ja mikä tahansa mielenterveyden häiriö olivat yhteydessä korkeampaan verenvuotoriskiin. Vähäisempi AK-hoidon käyttö selitti osin mielenterveyden häiriöitä sairastavien potilaiden heikompaa ennustetta. **Päätelmät**: Aivoinfarktien ehkäisyyn AK-hoidolla tulisi kiinnittää enemmän huomiota mielenterveyden häiriöitä sairastavien eteisvärinäpotilaiden kohdalla. Mielenterveyden häiriöitä sairastavilla potilailla on huonompi ennuste kuin muilla eteisvärinäpotilailla, ja mielenterveyden häiriöt ovat itsenäisesti yhteydessä suurentuneeseen verenvuodon ja kuoleman riskiin. Mielenterveyden häiriöt eivät kuitenkaan itsenäisesti lisää iskeemisen aivohalvauksen riskiä eteisvärinäpotilailla.

AVAINSANAT: Eteisvärinä, mielenterveyshäiriöt, antikoagulaatiohoito, hoitoon sitoutuminen, rytmikontrollihoidot, ennuste

Table of Contents

Abbreviations **8**

List of Original Publications **10**

1 Introduction **12**

2 Review of the literature **13**
2.1 Atrial fibrillation 13
2.1.1 Pathophysiology 13
2.1.2 Epidemiology and impact of atrial fibrillation 13
2.1.3 Symptoms of atrial fibrillation 14
2.2 Management of atrial fibrillation 15
2.2.1 Stroke prevention 15
2.2.1.1 Assessment of stroke risk 15
2.2.1.2 Assessment of bleeding risk 16
2.2.1.3 Oral anticoagulation 17
2.2.1.4 Left atrial appendage occlusion 19
2.2.1.5 Adherence to OAC therapy 19
2.2.2 Symptom management 20
2.2.2.1 Rate control 20
2.2.2.2 Rhythm control strategy 21
2.3 Mental health conditions and atrial fibrillation 23
2.3.1 Epidemiology 23
2.3.2 Symptoms of atrial fibrillation in patients with mental health conditions 24
2.3.3 Management of atrial fibrillation in patients with mental health conditions 25
2.3.4 Impact of mental health conditions on outcomes in patients with atrial fibrillation 28

3 Aims **31**

4 Materials and Methods **32**
4.1 Study population 32
4.2 Study ethics 33
4.3 Definitions 34
4.3.1 Mental health conditions 34
4.3.2 Baseline characteristics of the study cohort 34
4.3.3 Outcomes of interest 34
4.4 Statistical analysis 35

5 Results 37
5.1 Initiation of OAC therapy (I) 37
5.2 Implementation of NOAC therapy (II) 39
5.3 Persistence of NOAC therapy (III) 40
5.4 Use of rhythm control therapies (IV) 41
5.5 Risk of ischemic stroke and mortality (V) 42
5.6 Risk of bleeding (VI) 44

6 Discussion 46
6.1 Use of OAC therapy (I, II and III) 46
6.2 Use of rhythm control therapies (IV) 48
6.3 Outcomes (V and VI) 49
6.4 Strengths and limitations 51
6.5 Future implications 53

7 Conclusions 54

Acknowledgements 55

References 57

Original Publications 73

Abbreviations

AF	Atrial fibrillation
AAD	Antiarrhythmic drug
AAT	Antiarrhythmic therapy
$CHADS_2$	Congestive heart failure, Hypertension, Age ≥ 75, Diabetes mellitus, prior Stroke, transient ischemic attack, or thromboembolism (doubled)
CHA_2DS_2-VASc	Congestive heart failure, Hypertension, Age ≥ 75 (doubled), Diabetes mellitus, prior Stroke, transient ischemic attack, or thromboembolism (doubled), Vascular disease, Age 65 to 74, Sex category female
CI	Confidence interval
EARLY-AF	Early Aggressive Invasive Intervention for Atrial Fibrillation
EHRA	European Heart Rhythm Association
ESACOMP	European Society for Patient Adherence, Compliance, and Persistence
ESC	European Society of Cardiology
EMERGE	ESACOMP Medication Adherence Reporting Guidelines
FinACAF	Finnish AntiCoagulation in Atrial Fibrillation
GI	Gastrointestinal
HAS-BLED	Hypertension, Abnormal Liver or Renal Function, Stroke, Bleeding, Labile International Normalized Ratio, Elderly, Drugs or Alcohol
HR	Hazard ratio
IC	Intracranial
ICD-10	International Classification of Diseases, 10th revision
INR	International Normalized Ratio
IRR	Incidence rate ratio
LAAO	Left atrial appendage occlusion
NOAC	Non-vitamin K antagonist oral anticoagulant
MHC	Mental health condition
MPR	Medication possession ratio

OAC	Oral anticoagulant
OR	Odds ratio
RCT	Randomized controlled trial
SD	Standard deviation
SHR	Subdistribution hazard ratio
TTR	Time in therapeutic range
VKA	Vitamin K antagonist

List of Original Publications

This dissertation is based on the following original publications, which are referred to in the text by their Roman numerals:

I Jaakkola J, Teppo K, Biancari F, Halminen O, Putaala J, Mustonen P, Haukka J, Linna M, Kinnunen J, Tiili P, Aro AL, Hartikainen J, Airaksinen KEJ, Lehto M. The effect of mental health conditions on the use of oral anticoagulation therapy in patients with atrial fibrillation: the FinACAF study. *European Heart Journal – Quality of Care and Clinical Outcomes.* 2022 May 5;8(3):269-276.

II Teppo K, Jaakkola J, Airaksinen KEJ, Biancari F, Halminen O, Putaala J, Mustonen P, Haukka J, Hartikainen J, Luojus A, Niemi M, Linna M, Lehto M. Mental health conditions and adherence to direct oral anticoagulants in patients with incident atrial fibrillation: A nationwide cohort study. *General Hospital Psychiatry*. 2022 Jan-Feb;74:88-93.

III Teppo K, Jaakkola J, Airaksinen KEJ, Biancari F, Halminen O, Putaala J, Mustonen P, Haukka J, Hartikainen J, Luojus A, Niemi M, Linna M, Lehto M. Mental Health Conditions and Nonpersistence of Direct Oral Anticoagulant Use in Patients With Incident Atrial Fibrillation: A Nationwide Cohort Study. *Journal of the American Heart Association*. 2022 Mar 15;11(6):e024119.

IV Teppo K, Jaakkola J, Biancari F, Halminen O, Putaala J, Mustonen P, Haukka J, Linna M, Kinnunen J, Luojus A, Itäinen-Strömberg S, Penttilä T, Niemi M, Hartikainen J, Airaksinen KEJ, Lehto M. Mental health conditions and use of rhythm control therapies in patients with atrial fibrillation: a nationwide cohort study. *BMJ Open*. 2022 Aug 30;12(8):e059759.

V Teppo K, Jaakkola J, Biancari F, Halminen O, Putaala J, Mustonen P, Haukka J, Linna M, Kinnunen J, Tiili P, Kouki E, Penttilä T, Hartikainen J, Aro AL, Airaksinen KEJ, Lehto M. Mental health conditions and risk of first-ever ischaemic stroke and death in patients with incident atrial fibrillation: A nationwide cohort study. *European Journal of Clinical Investigation*. 2022 Sep;52(9):e13801.

VI Teppo K, Jaakkola J, Biancari F, Halminen O, Linna M, Putaala J, Mustonen P, Kinnunen J, Jolkkonen S, Niemi M, Hartikainen J, Airaksinen KEJ, Lehto M. Mental health conditions and bleeding events in patients with incident atrial fibrillation: A Finnish nationwide cohort study. *General Hospital Psychiatry*. 2022 Sep-Oct;78:117-122.

1 Introduction

Despite improvements in overall health and the emergence of new medical treatment possibilities, profound health disparities persist between groups defined by characteristics such as age, gender, ethnicity and socioeconomic status (Baptiste-Roberts et al., 2017; Chang, 2019; Thornton et al., 2016; Wheeler & Bryant, 2017). Advances in medical therapies are not equally available to all, considerably diminishing their potential overall benefit to the global population. Those most in need of effective treatment are often those for whom the therapies recommended in the most recent clinical practice guidelines are out of reach due to a range of medical, social and economic issues (Braveman et al., 2011; Krahn et al., 2015; Samuel et al., 2020).

Mental health conditions (MHCs) have long been stigmatized, leading to prejudice and discrimination against people who suffer from these disorders (Corrigan & Watson, 2002). Although stigma is not limited to MHCs, the public seems to have a much more negative attitude toward people with psychiatric disorders than those with physical illnesses (Corrigan et al., 2000; Socall & Holtgraves, 1992). Patients with MHCs face many barriers in healthcare access and often have undertreated somatic comorbidities, resulting in significantly increased morbidity and mortality (M. de Hert et al., 2009; Dickerson et al., 2003; Koponen & Lappalainen, 2015; Laursen et al., 2011).

Atrial fibrillation (AF), the most common sustained cardiac arrhythmia, is a major cause of ischemic stroke and is associated with impaired quality of life, dementia, heart failure and mortality (Benjamin et al., 1998; Björck et al., 2013; de Bruijn et al., 2015; Dorian et al., 2000; Friedman et al., 1968; Stewart et al., 2002; Wolf et al., 1991). The present study focuses on patients diagnosed with AF in Finland during 2007–2018 and investigates whether treatment and outcome disparities exist between patients with and without MHCs.

2 Review of the literature

2.1 Atrial fibrillation

2.1.1 Pathophysiology

Irregular heartbeat in patients with mitral stenosis was described in 1827, but it was not until 1909 that atrial fibrillation (AF) was first identified and recorded on an electrocardiogram by Thomas Lewis (Lewis, 1909; Lip & Beevers, 1995). AF is characterized by a lack of coordinated electrical impulses from the sinus node to the atrioventricular node and synchronous atrial and ventricular contractions encountered in normal sinus rhythm. Instead, in AF, chaotic high-frequency electrical activity of the atrium results in dyssynchronous atrial contractions and irregular ventricular excitation.

The genesis of AF requires a vulnerable atrial substrate, which relates to left atrial dilatation, fibrosis and myopathy, and the formation and composition of this substrate varies depending on comorbid conditions, genetics, sex, and lifestyle-related factors (Packer, 2020; Staerk et al., 2017). Clinical risk factors for atrial myopathy and, consequently, for the risk of developing AF include clinical settings of prolonged hemodynamic stress, such as hypertension and valvular heart disease, as well as metabolic and inflammatory disorders such as obesity, diabetes, and rheumatoid arthritis (Packer, 2020).

2.1.2 Epidemiology and impact of atrial fibrillation

AF is the most common form of sustained cardiac arrhythmia, with a prevalence as high as 4.1% in the general population (Dai et al., 2021; Lehto, et al., 2022). Advancing age is a prominent risk factor for AF, and the overall prevalence of AF is projected to increase significantly in the future owing to extended longevity in the general population as well as advances in AF diagnostics (Dai et al., 2021; Krijthe et al., 2013). One-third of persons 55 years or older will develop AF during their lifetime, and in the European Union, the number of adults over 55 with AF is predicted to more than double from 2010 to 2060 (Krijthe et al., 2013; Staerk et al.,

2018). Moreover, even these seemingly high figures may be underestimations, since arrhythmia is often asymptomatic and undiagnosed (Savelieva & Camm, 2000).

Although AF is often considered to be a relatively benign condition, it is in fact associated with severe complications. Importantly, AF is a leading cause of ischemic stroke, which often has devastating impacts on the lives of individuals through impairments in physical, psychological and social functions (Friedman et al., 1968; lo Buono et al., 2017; Wolf et al., 1991). Moreover, ischemic strokes related to AF are usually more severe than strokes without AF. The presence of AF in patients suffering ischemic strokes has been associated with larger infarcted areas, more severe neurological deficits, longer hospital stays and higher mortality, as well as higher healthcare costs (Brüggenjürgen et al., 2007; Jørgensen et al., 1996; Kimura et al., 2005; Winter et al., 2009). Hence, the prevention of ischemic strokes is of utmost importance in the management of AF. Additionally, AF is associated with heart failure, dementia, frequent hospitalizations and a 1.5–3.5 fold increase in all-cause mortality (Benjamin et al., 1998; Kalantarian et al., 2013; Kotecha et al., 2016; Meyre et al., 2019; Stewart et al., 2002; Wang et al., 2003).

In addition to this considerable burden of AF on individual patients, it is estimated that up to 2.6% of total annual healthcare expenditure is associated with AF in European countries, with costs mainly deriving from hospitalizations and stroke complications (Ball et al., 2013; Cotté et al., 2016; Ringborg et al., 2008; Stewart et al., 2004). In Finland alone, the estimated total annual healthcare costs of all patients with AF are as high as 2 billion euros (Rissanen et al., 2021). Furthermore, due to the projected increase in AF prevalence over the coming decades, AF places an increasingly critical financial burden on healthcare systems (Krijthe et al., 2013).

2.1.3 Symptoms of atrial fibrillation

Symptoms related to AF range from none to disabling, and the prevalence of asymptomatic presentation among AF patients has varied between 10% and 40% in previous reports, depending on the screening methods used and the definitions of symptoms (Mccabe et al., 2015; Siontis et al., 2016; Steg et al., 2012). However, AF often considerably impairs patients' quality of life through arrhythmia-related psychological distress and exercise intolerance (Gehi et al., 2012; Steg et al., 2012). Other common symptoms attributable to AF include palpitations, chest pain, dyspnoea, fatigue and dizziness (Rienstra et al., 2012).

Identification of the symptoms of AF and the actual mechanisms underlying them is complicated by the fact that AF frequently occurs with other cardiovascular comorbidities, such as heart failure, valve diseases and coronary artery disease. Indeed, many of these commonly encountered comorbidities may present with

similar symptoms as AF. Moreover, these conditions may not only mimic but also aggravate symptoms of AF (Rienstra et al., 2012). Thus, symptoms related to AF are often multifactorial and result from both the direct and indirect effects of arrhythmia. Pathways linking arrhythmia with symptoms include irregular and fast heartrate and loss of atrial contraction and atrioventricular synchrony, leading to decreased cardiac output, impaired myocardial perfusion and autonomic dysfunction (Rienstra et al., 2012). Additionally, patients' emotional state has been shown to modulate symptom burden. Negative affectivity, psychological distress, depression and anxiety have been associated with increased symptom perception (Thompson et al., 2014; Ladwig et al., 2020; van der Velden et al., 2022).

Various symptom scores and questionnaires have been developed to provide a more accurate objective assessment of AF -related symptoms and the effects of therapies. While most of these scales are used for research purposes, a few, such as the European Heart Rhythm Association (EHRA) symptom score, have also been adopted for the clinical management of patients with AF. The simple EHRA score classifies patients into categories ranging from no symptoms in EHRA class I to disabling symptoms in EHRA class IV (Hindricks et al., 2021; Rienstra et al., 2012).

2.2 Management of atrial fibrillation

2.2.1 Stroke prevention

2.2.1.1 Assessment of stroke risk

Several studies over the past few decades have firmly established the causative role of AF in cardioembolic strokes and other thromboembolisms (Hinton et al., 1977; Stewart et al., 2002; Wolf et al., 1991). The pathological thrombus formation in AF is multifactorial, fulfilling Virchow's triad of thrombogenesis, including abnormal blood flow and stasis in the left atrium and left atrial appendage, structural defects in the atrial tissue, and abnormalities in haemostatic activation and inflammatory responses (Ding et al., 2020).

The thrombus formation and eventual risk of cardioembolic stroke vary considerably among AF patients according to individual patient characteristics and comorbidities, and identifying patients at high risk of stroke is vital in the management of AF and effective stroke prevention (Hindricks et al., 2021; Lip et al., 2010). To quantify patient's individual stroke risk and guide treatment decisions, several risk stratification tools have been proposed in recent decades (Fang et al., 2008). In 2001, earlier risk stratification schemes were merged to form the $CHADS_2$-score, which was subsequently adopted in clinical guidelines (Fuster et al., 2006; Gage et al., 2001).

However, while the $CHADS_2$-score was useful in detecting patients at high risk of stroke, it lacked accuracy in detecting patients at low risk. Indeed, detecting these low-risk patients is also important in the clinical decision making of stroke prevention therapies to avoid possible adverse events caused by unnecessary therapies for patients not requiring stroke prevention (Olesen et al., 2012). Therefore, a more precise risk stratification scheme, the CHA_2DS_2-VASc-score, was published in 2010 (Lip et al., 2010). This new risk score was more effective in characterizing low-risk patients and thus more useful in clinical decision making (Lip et al., 2010; Olesen et al., 2012).

The CHA_2DS_2-VASc-score was thereafter included in the clinical guidelines for the management of AF and is currently the most commonly used stroke risk assessment tool (Camm et al., 2012; Hindricks et al., 2021). Risk points in the CHA_2DS_2-VASc-score are assigned for congestive heart failure, hypertension, age ≥ 75 (2 points), diabetes mellitus, prior stroke, transient ischemic attack or thromboembolism (2 points), vascular disease, age 65 to 74 and sex (female) (Lip et al., 2010). The annual risk of stroke according to the total CHA_2DS_2-VASc-score is depicted in **Table 1**.

Table 1. Adjusted annual risk of stroke according to the total CHA_2DS_2-VASc score (Lip et al. 2010).

Total score	CHA_2DS_2-VASc
0	0.0%
1	1.3%
2	2.2%
3	3.2%
4	4.0%
5	6.7%
6	9.8%
7	9.6%
8	6.7%
9	15.2%

2.2.1.2 Assessment of bleeding risk

While assessing the individual risk of ischemic stroke is vital when deciding who needs interventions for stroke prevention, concurrent evaluation of a patient's risk of bleeding is similarly important to minimize the potential harms of preventive therapies for stroke. An inherent downside of antithrombotic therapies to prevent stroke is the increased risk of bleeding. Thus, the potential benefits of stroke prevention must be balanced against the risk of severe bleeding events, particularly

intracranial bleeding. Therefore, several bleeding risk stratification scores have been developed to guide clinical treatment decisions (Hindricks et al., 2021).

The most commonly used and widely adopted tool in quantifying bleeding risk is the HAS-BLED-score, which includes the following factors: uncontrolled hypertension (systolic blood pressure >160 mmHg), abnormal liver function or renal insufficiency, history of stroke, bleeding history or predisposition to bleeding, labile international normalized ratio (INR), >65 years of age and concomitant use of drugs or alcohol (Pisters et al., 2010; ESC, 2020). The HAS-BLED score has been validated in a number of studies, but has shown only moderate predictive value for major bleeding events (c-statistics 0.60–0.80) (Apostolakis et al., 2013; Roldán et al., 2013). In patients identified to be at risk of bleeding, management of modifiable bleeding risk factors, such as adequate treatment of hypertension, as well as more frequent follow-up to effectively identify signs of bleeding, is important to enable safe stroke prevention (Hindricks et al., 2021). Indeed, the main purpose of bleeding risk assessment is not to identify patients in whom stroke preventive therapies should be withheld, since these patients often also have a high risk of ischemic stroke due to overlapping risk factors for both ischemic stroke and bleeding. In fact, even in patients with a high risk of bleeding, anticoagulant therapy is usually beneficial (Friberg et al., 2012).

2.2.1.3 Oral anticoagulation

Complex homeostasis in the human body maintains a balance between thrombus formation and dissolution. This multifaceted system is carefully regulated, and during physiological circumstances, homeostasis favours clot dissolution, and spontaneous clot formation is inhibited (Dahlbäck, 2000). However, a prothrombotic state prevails in the presence of AF and its associated comorbidities (Ding et al., 2020). To prevent pathological thrombus formation and cardioembolic strokes in patients with AF, oral anticoagulant therapy (OAC) is used (Hindricks et al., 2021). The most recent European Society of Cardiology (ESC) guidelines on the management of AF state that OAC therapy should be considered in patients with a CHA_2DS_2-VASc-score of 1 for men and 2 for women, and that OAC therapy is recommended for AF patients with a CHA_2DS_2-VASc-score over 1 in men and over 2 in women (Hindricks et al., 2021).

Until recently, vitamin K antagonists (VKAs) have been the only OAC available for stroke prevention. The efficacy of warfarin, the most commonly used VKA, was initially demonstrated in a series of randomized controlled trials (RCTs) three decades ago (Connolly et al., 1991; Ezekowitz et al., 1992; McBride, 1991; Petersen et al., 1989). When compared with a placebo, the original trials and subsequent comprehensive meta-analyses demonstrated a two-thirds risk reduction in ischemic stroke and a 26% reduction in all-cause mortality among patients receiving warfarin

(Hart et al., 2007; Lip & Edwards, 2006). In addition to this clear benefit over a placebo, warfarin was confirmed to be superior to aspirin in stroke prevention (Hart et al., 2007; Petersen et al., 1989).

Warfarin and other VKAs inhibit the function of the vitamin K-dependent epoxide reductase complex in the liver, resulting in reduced activity of vitamin K-dependent coagulation factors (II, VII, IX and X) and consequently decreased thrombus formation (Ageno et al., 2012). Regular monitoring of the anticoagulation effect of warfarin with INR laboratory testing is a prerequisite for successful and safe warfarin therapy. In AF patients without a mechanical mitral valve or mitral stenosis, the optimal INR range for both safety and efficacy is between 2 and 3, with the risk of stroke increasing in INR values below 2 and the risk of bleeding increasing in values above 3 (Hylek et al., 2003).

In the past decade, the emergence of non-vitamin K antagonist oral anticoagulants (NOACs), i.e., dabigatran, apixaban, edoxaban and rivaroxaban, has revolutionized the landscape of stroke prevention in AF. When compared to the mechanism of action of VKAs, the pharmacodynamic target of all NOACs is located "downstream" in the coagulation cascade: dabigatran is a direct thrombin inhibitor, and apixaban, edoxaban and rivaroxaban are factor Xa inhibitors (Connolly et al., 2009; Giugliano et al., 2013; Granger et al., 2011; Patel et al., 2011). While the acronym NOAC seems to be the most widely accepted term when referring to these agents collectively, due to their mechanism of action and their novelty in contrast to VKAs, they are also often called "direct oral anticoagulants", "novel oral anticoagulants", and "target-specific oral anticoagulants".

Unlike VKAs, NOACs do not require systematic dose monitoring, and they provide a fast and stable anticoagulation effect with fewer drug interactions, dietary precautions and other laboratory test requirements (Hindricks et al., 2021). A meta-analysis pooling the evidence from the original NOAC trials reported a 19% (95% confidence interval (CI) 9%–27%) lower stroke or systemic embolism risk with NOACs compared with warfarin. Moreover, NOACs were associated with lower all-cause mortality and risk of haemorrhagic stroke or intracranial haemorrhage, while the risk of gastrointestinal bleeding was higher with NOACs than with warfarin (Ruff et al., 2014).

Regarding the bleeding risk caused by OAC therapy, in RCTs, the annual risks of major bleeding and intracranial bleeding in patients receiving warfarin have been reported as 3.09–3.43% and 0.70–0.85%, respectively (Connolly et al., 2009; Giugliano et al., 2013; Granger et al., 2011; M. R. Patel et al., 2011). Nevertheless, the benefits of OAC therapy in stroke prevention outweigh the risk of adverse bleeding events in most AF patients (Friberg et al., 2012).

Due to their superior efficacy and safety, NOACs have been recommended over VKAs as the first choice for OAC therapy in the ESC guidelines on the management of AF since 2016 (Hindricks et al., 2021; P. Kirchhof et al., 2016).

2.2.1.4 Left atrial appendage occlusion

In patients with a perceived high bleeding risk or contraindications for OAC therapy, left atrial appendage occlusion (LAAO) is an alternative method for the prevention of cardioembolic strokes (Boersma et al., 2017). The rationale for this procedure is based on evidence that up to 90% of cardioembolisms attributable to AF originate from the left atrial appendage (Hindricks et al., 2021). The percutaneously implantable closure devices mechanically obstruct the left atrial appendage and therefore stagnation of blood and clot formation in the appendage are prevented (Safavi-Naeini & Rasekh, 2018). RCTs comparing LAAO with VKA or NOAC therapy have demonstrated that the procedure has a similar ability to prevent ischemic strokes but is associated with a lower rate of haemorrhagic stroke and both cardiovascular and all-cause mortality among patients with AF and high bleeding and ischemic stroke risk. Furthermore, a Nordic observational study in patients with AF and prior intracranial bleeding reported that LAAO was associated with a substantially lower risk of the composite endpoint of all-cause death, ischemic stroke and major bleeding when compared to standard care (hazard ratio of 0.16 (95% CI 0.07–0.37)) (Nielsen-Kudsk et al., 2017). An alternative to percutaneous LAAO is surgical left atrial appendage exclusion, but this is performed during open heart surgery and only limited control trial data is available on its efficacy and safety (Tsai et al., 2015). Currently, the ESC guidelines recommend considering percutaneous LAAO in AF patients with a clear indication for stroke prevention but a contraindication for long-term OAC therapy (Hindricks et al., 2021).

2.2.1.5 Adherence to OAC therapy

Medication adherence is essential in the prevention and treatment of chronic conditions, and suboptimal adherence is frequently a major barrier to effective pharmacotherapy. Although often unrecognized, poor adherence is in fact highly prevalent and a commonly neglected aspect in medical therapies (Osterberg & Blaschke, 2005; Rand, 1993; WHO, 2003). In a large meta-analysis of statin users aged 65 years and over, only 60% of patients had good adherence to statin therapy at one-year follow-up (Ofori-Asenso et al., 2018). Another meta-analysis assessing the use of antihypertensives, statins, antidiabetics and antidepressants reported that 15% of patients never fill the first dispensation of the prescription medication (Lemstra et al., 2018).

Reporting of research on medication adherence has often been suboptimal, and inconsistency in the methods and definitions used has hampered the interpretation and comparison of results. Hence, the European Society for Patient Adherence, Compliance and Persistence (ESACOMP) has developed the ESACOMP Medication Adherence Reporting Guidelines (EMERGE) (de Geest et al., 2018). These guidelines are based on a previously introduced taxonomy, which defines medication adherence

as “the process by which patients take their medications as prescribed” (Vrijens et al., 2012). Medication adherence is divided into three distinct yet interrelated phases: initiation, implementation and persistence (de Geest et al., 2018).

Initiation refers to the patient starting the recommended treatment, that is, whether the patient takes the first dose of the prescribed medication. Implementation refers to how the patients’ actual dosing matches the prescribed dosing between the first and last administered doses. Depending on the available data and the aims of the research, several measures can be utilized to quantify treatment implementation (Vrijens et al., 2012). Often, implementation is assessed using pharmacy claims data, and the most common metrics are the medication possession ratio (MPR) and the proportion of days covered (Malo et al., 2017). Both metrics calculate the number of redeemed doses compared to prescribed doses over a certain period of time (Malo et al., 2017). The third phase of medication adherence, persistence, quantifies the length of time from treatment initiation until the last dose (Vrijens et al., 2012).

Stroke prevention with OACs in AF is dependent on medication adherence in a real-world setting. Several observational studies have reported that poor OAC therapy implementation is associated with poor outcomes in patients with AF (Salmasi et al., 2020). Concerning VKA therapy, poor treatment implementation is reflected in the INR and time in therapeutic range (TTR) values used to monitor the anticoagulation effect, and low INR and TTR have been associated with an increased risk of stroke and mortality (Hylek et al., 2003; Lehto et al., 2017). Similarly, poor implementation of NOAC therapy has been shown to increase the risk of stroke and mortality (Salmasi et al., 2020). Kim et al. observed that patients with AF and good adherence to NOACs in the implementation phase had a 27% lower adjusted risk of stroke or systemic embolism and a similar risk of bleeding when compared to patients with poor adherence (Kim et al., 2020). Hence, adequate implementation of NOAC therapy seems to improve outcomes without increasing bleeding risks. Likewise, Komen et al. reported that poor treatment implementation and persistence are associated with increased stroke risk (Komen, Heerdink, et al., 2021). Furthermore, two studies measuring the economic impacts of OAC adherence showed that poor implementation of OAC therapy is associated with higher rates of inpatient and emergency room encounters, longer hospital stays and higher medical costs (Casciano et al., 2013; Deshpande et al., 2018).

2.2.2 Symptom management

2.2.2.1 Rate control

Rate control refers to therapeutic interventions that reduce the rapid ventricular rate commonly present in patients with AF. Rate control is central to AF management, and it is often sufficient to improve symptoms related to AF (Hindricks et al., 2021).

Pharmacological rate control with beta-blockers, digoxin, non-dihydropyridine calcium channel blockers or combination therapy is the primary method for lowering heart rate. Additionally, some antiarrhythmic drugs (AADs), such as amiodarone and sotalol, can be used in rate control owing to their rate-limiting effects, although AADs are mainly indicated for rhythm control (Hindricks et al., 2021).

The ideal target heart rate is unclear, and no difference in clinical outcomes was observed in an RCT comparing a strict rate target under 80 beats per minute and a lenient target under 110 beats per minute (van Gelder et al., 2010). Thus, lenient rate control is recommended as the initial target in the current guidelines unless patients' symptoms require stricter rate control (Hindricks et al., 2021).

If sufficient rate control is not achieved pharmacologically, ablation of the atrioventricular node and pacemaker implantation are the last resort to control the ventricular rate. This procedure is relatively simple and safe, with a low long-term mortality risk and a low complication rate (Lim et al., 2007).

2.2.2.2 Rhythm control strategy

Rhythm control strategy refers to interventions that restore and sustain sinus rhythm. It encompasses a variety of treatment options, including cardioversion, AADs and catheter ablation, either used individually or in combination therapy.

According to the current guidelines on AF management, the primary indication for rhythm control therapies is symptoms related to AF (Hindricks et al., 2021). This recommendation is based on several RCTs that did not show better outcomes with rhythm control compared to the rate control strategy (Sethi et al., 2017). Therefore, rhythm control therapies are mainly reserved for patients who remain symptomatic after adequate rate control or for patients who are hemodynamically unstable due to AF. However, since the symptoms related to AF are at times difficult to distinguish definitively, an attempt to restore sinus rhythm is often recommended as the initial step in evaluating symptom relief when the actual symptom burden is uncertain (Hindricks et al., 2021). Although reduction of symptoms and improvement of quality of life are the main objectives of the rhythm control strategy, recent studies have also suggested outcome benefits of rhythm control. In an RCT by Kirchhof et al. (2020), early use of AADs or catheter ablation within the first year of AF diagnosis was associated with a reduction in the composite outcome of cardiovascular death, stroke or hospitalization with heart failure or acute coronary syndrome. Additionally, in selected patients with AF and heart failure, catheter ablation has been shown to improve the left ventricular ejection fraction and decrease hospitalizations and mortality (di Biase et al., 2016; Marrouche et al., 2018).

Cardioversion is often the initial method for restoring sinus rhythm in patients with AF and can be performed either pharmacologically or electrically. Synchronized direct

current electrical cardioversion is suggested in haemodynamically unstable patients, while both pharmacological and electrical cardioversions may be considered in stable patients (Hindricks et al., 2021). Pharmacological cardioversion can be performed without sedation, but it is less effective than electrical cardioversion (Boriani et al., 2004; Furniss & Sneyd, 2015). Moreover, the spontaneous restoration rate of recent onset AF is relatively high, with 52–77% of patients converting spontaneously to sinus rhythm within 48 hours (Pluymaekers et al., 2021). Thus, a wait-and-watch strategy can be considered in patients with recent onset AF, particularly among otherwise healthy patients on OAC therapy with only mild symptoms, since in the event of spontaneous recovery of sinus rhythm, the potential harms of cardioversion can be safely avoided (Airaksinen, 2022).

In pharmacological cardioversion, the choice of drug is based on the presence and severity of underlying heart disease. The class 1c drugs of the Vaughan Williams classification of AADs, such as flecainide and propafenone, are recommended for patients without left ventricular hypertrophy, systolic dysfunction or ischemic heart disease, and provide a relatively rapid, efficient and safe recovery of sinus rhythm (Lavalle et al., 2021; Lei et al., 2018; Markey et al., 2018). Amiodarone, mainly reserved for patients with heart failure, has a slower and more limited effect, but its rate-lowering properties are often beneficial in the acute phase of AF (Letelier et al., 2003). Vernakalant is the most effective and rapid cardioverting drug and can also be used for patients with mild heart failure and ischemic heart disease (Bash et al., 2012). Overall, however, the success rate of pharmacological cardioversion is less satisfactory than that of electrical cardioversion (Airaksinen, 2022).

After restoration of sinus rhythm, long-term AAD therapy is often needed to prevent future AF paroxysms. As with all rhythm control therapies, the objective of AAD therapy is to improve AF-related symptoms. Rather than eliminating AF recurrences, AADs at best reduce their rate by approximately doubling the time maintained in sinus rhythm (Lafuente-Lafuente et al., 2015). Currently, flecainide, dronedarone and amiodarone are the most frequently used AADs for long-term treatment (Hindricks et al., 2021). AADs predispose patients to both cardiac and extracardiac side effects, and particularly in the use of amiodarone, regular surveillance of liver, lung and thyroid toxicity is required (Epstein et al., 2016). Therefore, in the clinical decision making of long-term AAD therapy initiation, symptom burden, potential AAD side effects and interactions, and patient preferences should be balanced.

In addition to cardioversion and AADs, catheter ablation is a well-established and powerful tool for preventing AF recurrence (Arbelo et al., 2017). The ablation procedure is based on the elimination of the substrates triggering AF paroxysms, most commonly by pulmonary vein isolation with radiofrequency or cryo-balloon technology (Mujović et al., 2017). Catheter ablation is relatively safe, and its efficacy in preventing AF is superior to long-term AAD therapy (Nyong et al., 2016). Indeed,

in the recent Early Aggressive Invasive Intervention for Atrial Fibrillation (EARLY-AF) trial, catheter ablation was found to be superior to AADs as the initial approach to preventing AF recurrence (Andrade et al., 2020). While surgical AF ablation is an alternative to less invasive catheter-based techniques, it is used only concomitantly with other heart surgery (Gammie et al., 2008; Hindricks et al., 2021). The main indications and prerequisites for catheter ablation therapy are arrhythmia-related symptoms. This is based on evidence from previous RCTs comparing catheter ablation with medical therapy, confirming improvement in quality of life and reduction in AF symptom burden in patients treated with catheter ablation (Blomström-Lundqvist et al., 2019; Mark et al., 2019). However, since most previous RCTs have not shown significant outcome benefits of ablation therapy, the role of catheter ablation in patients with AF has largely remained a symptomatic treatment. Nevertheless, as stated above, in selected patients with AF and a reduced left ventricular ejection fraction, two RCTs have associated a decrease in hospitalizations and all-cause mortality with ablation therapy (di Biase et al., 2016; Marrouche et al., 2018). Hence, catheter ablation may be considered for patients with heart failure with a reduced ejection fraction selected for rhythm control management, especially if tachycardia-induced cardiomyopathy is suspected (Raymond-Paquin et al., 2018). Furthermore, ongoing trials are investigating the impact of catheter ablation on major cardiovascular events (Kirchhof et al., 2013).

Interventions and medications that impact atrial remodelling may support the maintenance of sinus rhythm in addition to the conventional rhythm control therapies described above. A recent trial demonstrated that the evaluation and targeted treatment of underlying comorbidities reduces the risk of AF paroxysms (Rienstra et al., 2018). Statins, renin-angiotensin-aldosterone system inhibitors and beta-blockers have also been proposed to possess properties that could be helpful in the prevention of AF, but RCTs have been unable to demonstrate a robust reduction in the AF paroxysm rate with these medications (Savelieva et al., 2011b, 2011a). Additionally, treatment of obstructive sleep apnoea, weight loss and abstinence from alcohol have been shown to significantly reduce arrhythmia recurrences (Abed et al., 2013; Qureshi et al., 2015; Voskoboinik et al., 2020).

2.3 Mental health conditions and atrial fibrillation

2.3.1 Epidemiology

MHCs are characterized by disturbances in individuals' emotional regulation, cognition or behaviour, which usually cause significant distress or impairment in important areas of functioning (Porteri, 2010). MHCs are exceedingly prevalent. The 12-month and lifetime prevalence rates of any MHC in the United States have been

reported to be as high as 26% and 46%, respectively (Alonso & Lépine, 2007; Kessler, Berglund, et al., 2005; Kessler, Wai, et al., 2005). Worldwide the most common single disorder with a lifetime risk of 17% is major depression and the most common disorder class is anxiety disorders with a lifetime risk of 29% (Kessler, Berglund, et al., 2005). In Finland, the reported 12-month prevalence figures for depression and anxiety disorder have been 6% and 4%, respectively, and the lifetime prevalence rates for bipolar disorder, schizophrenia, and any psychotic disorder 0.5%, 1% and 3%, respectively (Markkula & Suvisaari, 2017; Perälä et al., 2007; Pirkola et al., 2005; J. Suvisaari et al., 2009).

According to the World Health Organization, the global prevalence of MHCs is increasing, owing mainly to demographic changes (World Health Organization, 2022). Indeed, the Global Burden of Disease 2019 Study reported that the age-standardized global burden of mental disorders actually remained consistent between 1990 and 2019 (GBD 2019 Mental Disorders Collaborators, 2022). Thereafter, however, the COVID-19 pandemic seems to have triggered an increase in the prevalence of mental disorders (Santomauro et al., 2021).

In patients with AF, MHCs are likewise common, with prevalence estimates ranging from 25% to 50% (D. Patel et al., 2013; Thrall et al., 2007). The most commonly encountered specific psychiatric comorbidities among the elderly, in whom AF is common, are depression, anxiety disorders and schizophrenia (GBD 2019 Mental Disorders Collaborators, 2022). Interestingly, psychological distress and depression have also been associated with an increased incidence of AF (Fenger-Grøn et al., 2019; Ladwig et al., 2020). Some observational findings have also suggested that the use of antidepressants may increase the risk of AF (Buff et al., 1991; Fenger-Grøn et al., 2019).

2.3.2 Symptoms of atrial fibrillation in patients with mental health conditions

The relationship between the symptoms of AF and MHCs is complex and often bidirectional. On the other hand, depression and anxiety disorders have been reported to substantially amplify AF symptom perception (Gehi et al., 2012; Thompson et al., 2014; von Eisenhart Rothe et al., 2015). These mental disorders have also been associated with an increased likelihood of seeking care for the management of AF (Gehi et al., 2012). In fact, the existing literature mainly reports findings of a higher AF symptom burden among patients with MHCs, and there are no reports of MHCs ameliorating the perception of AF symptoms. On the other hand, AF may also augment psychological distress, and successful catheter ablation for AF has even been associated with a decrease in depression and anxiety symptoms (D. Patel et al., 2013; Sang et al., 2013; Yu et al., 2012). Anxiety and depression have also been

shown to increase the risk of AF recurrence after catheter ablation (Yu et al., 2012). Furthermore, reflecting the multifactorial background of symptom perception of both MHCs and AF, psychotherapy for the treatment of depression has been shown to mitigate symptoms of AF and improve overall quality of life in patients suffering from both depression and AF (Shan et al., 2022).

2.3.3 Management of atrial fibrillation in patients with mental health conditions

Patients with MHCs face several barriers to receiving optimal medical treatment for their somatic comorbidities. Previous research has indicated that patients suffering from MHCs are often undertreated for their somatic comorbidities (Druss et al., 2000; Vahia et al., 2008). Druss et al. observed that among patients hospitalized for acute myocardial infarction, those with psychiatric comorbidities were considerably less likely to undergo invasive coronary revascularization procedures than those without psychiatric comorbidity (Druss et al., 2000). Similarly, patients with severe mental illnesses have been shown to face disparities in cancer treatment, leading to higher mortality rates (Manderbacka et al., 2017). Suboptimal medication adherence often further impairs the potential benefits of initiated therapies in this vulnerable patient group (Hamieh et al., 2021), and several studies have associated MHCs with poor adherence to medical therapies for somatic comorbidities (Holvast et al., 2019; Levin et al., 2016; May et al., 2010; Phan, 2016).

Regarding the management of AF, previous studies have demonstrated treatment shortfalls among patients with MHCs. Characteristics of the studies assessing the impact of MHCs on the prevalence and quality of OAC therapy in patients with AF are summarized in **Table 2**. Signs of lower use of OAC therapy among patients with MHCs than among those without MHCs were first reported in a few small observational studies (Sánchez-Barba et al., 2013; G. A. Walker et al., 2011). Thereafter, a larger study by Schmitt et al., conducted among patients with AF treated in the Veterans Health Administration in the United States, observed that those with anxiety disorders or psychotic disorders were substantially less likely to receive warfarin therapy than those without MHCs (Schmitt et al., 2015). More recently, three Danish cohort studies, also covering a small number of patients receiving NOAC therapy in addition to patients receiving warfarin, similarly demonstrated a lower rate of OAC therapy initiation among those suffering from depression, bipolar disorder or schizophrenia (Fenger-Grøn et al., 2020, 2021; Højen et al., 2022).

Among patients receiving warfarin, the quality of treatment as measured by TTR has been shown to be worse in patients with MHCs than among patients without MHCs (Baumgartner et al., 2018; Diug et al., 2011; Paradise et al., 2014; Razouki et al., 2014; Rose et al., 2010). Additionally, depression has been associated with non-

adherence to NOAC therapy in one small Turkish questionnaire-based cross-sectional study (Emren et al., 2018). On the other hand, a study conducted in Japan found no association between self-reported depression and NOAC adherence (Suzuki et al., 2017). Otherwise, data on the impact of MHCs on the implementation or persistence of NOAC therapy in patients with AF is lacking.

Regarding the use of rhythm control therapies for AF, there is a complete paucity of information on possible treatment disparities between patients with and without MHCs.

Table 2. Characteristics of studies reporting the impact of mental health conditions on the prevalence and quality of oral anticoagulant therapy in patients with atrial fibrillation (Modified from Teppo et al. 2021).

Use of OAC therapy						
Study	**Country**	**Study design**	**No. of patients**	**Study interval**	**MHC**	**Effect on OAC use**
De Breucher et al. 2010	Belgium	Retrospective cohort study	768	2006–2008	Depression	No effect[5]
Denoel et al. 2014	Belgium	Cross-sectional study	142	2011–2012	GDS >1	0.72 (0.35–1.46)[4]
Fenger-Grøn et al. 2020	Denmark	Retrospective cohort study	147,162[2]	2005–2016	Depression	−4.2% (−4.7 to −3.8)*[3]
Fenger-Grøn et al. 2021	Denmark	Retrospective cohort study	147,810[2]	2005–2016	Bipolar disorder Schizophrenia	−5.3% (−7.9% to −2.6%)*[3] −15.5% (−19.3% to −11.7%)*[3]
Højen et al. 2022	Denmark	Retrospective cohort study	238,714	2000–2017	Schizophrenia	−19.4% (−23.6% to −15.3%)*[6]
Saczynski et al. 2020	USA	Cross-sectional study	1,244	2016–2018	Depression	0.79 (0.49–1.27)[1]
Sánchez-Barba et al. 2013	Mexico	Cross-sectional study	137	2008–2013	GDS >5	0.19 (0.07–0.54) *[1]
Schmitt et al. 2015	USA	Retrospective cohort study	125,670	2004	Any MHC Anxiety disorders Psychotic disorders Depression PTSD Other MHC	0.90 (0.87–0.94) *[1] 0.86 (0.80–0.93) *[1] 0.77 (0.65–0.90) *[1] 0.96 (0.91–1.02)[1] 0.99 (0.84–1.17)[1] 1.05 (0.92–1.19)[1]
Søgaard et al. 2017	Denmark	Retrospective cohort study	253,741	2000–2015	Severe depression, bipolar disorder and schizophrenia	Lower rate of OAC therapy initiation[5]
Walker et al. 2011	USA	Retrospective chart review	296	2003	Any MHC	0.42 (0.22–0.77) *[1]
Quality of OAC therapy						
Study	**Country**	**Study design**	**No. of patients**	**Study interval**	**Investigated association and findings**	
Baumgartner et al. 2018	USA	Retrospective cohort study	25,570	2004–2007	MHC and TTR%[10]	
					No anxiety or depression Anxiety Depression Anxiety and depression	57% 57% 52%* 53%*

Diug et al. 2011	Australia	Case–control study	157 cases 329 controls	2008–2009	GDS ≥2 and INR ≥6.0	2.1 (1.3–3.5)[9]*
Emren et al. 2017	Turkey	Cross-sectional study	2,738	2015–2016	Depression and poor NOAC adherence	1.94 (1.47–2.57)[9]*
Paradise et al. 2014	USA	Retrospective cohort study	103,897	2007–2008	MHC and TTR %[7]	
					Anxiety disorder	0.18%
					Bipolar disorder	−2.63%*
					Depression	−2.26%*
					PTSD	−0.01%
					Schizophrenia	−0.36%
					Other psychotic disorders	−2.29%*
Razouki et al. 2014	USA	Retrospective cohort study	103,897	2006–2008	MHC and percent time below and above INR target[7]	
					Anxiety disorder	Below +0.03 Above +0.07
					Bipolar disorder	Below +3.19* Above +0.68
					Depression	Below +2.01* Above +0.43*
					PTSD	Below +0.37 Above -0.53
					Schizophrenia	Below -0.78 Above +0.036
					Other psychotic disorders	Below +2.91 Above +0.54
Rose et al. 2010	USA	Retrospective cohort study	124,619	2006–2008	MHC and TTR %[7]	
					Alcohol abuse	−5.4 (−5.9 to −4.9) *
					Anxiety disorder	−0.2 (−0.6 to −0.3)
					Bipolar disorder	−1.8 (−2.7 to −1.0) *
					Major depression	−2.0 (−2.3 to −1.6) *
					PTSD	+0.4 (−0.2 to 0.9)
					Schizophrenia	+0.8 (−0.4 to 2.0)
					Substance abuse (non-alcohol)	−2.4 (−3.2 to −1.7) *
Suzuki et al. 2017	Japan	Questionnaire survey	378	2014	Self-reported depression and adherence	0.74 (0.26–2.64)[8]
Walker et al. 2011	USA	Retrospective chart review	296	2011–2012	Any MHC and INR >5	15.9 (1.6–154.1)[11]

[1]Adjusted odds ratio, [2]Incident AF patients,[3]Adjusted proportion difference,[4]Odds ratio,[5]Risk estimate not reported,[6]Adjusted risk difference,[7]Adjusted effect (95% confidence interval) ,[8] Hazard ratio (95% confidence interval),[9]Odds ratio (95% confidence interval),[10]Absolute TTR value,[11]Adjusted odds ratio (95% confidence interval). * $p < 0.05$. Abbreviations: NOAC, novel oral anticoagulant; GDS, Geriatric Depression Scale; INR, international normalized ratio; MHC, mental health condition; OAC, oral anticoagulation; PTSD, post-traumatic stress disorder; TTR, time in therapeutic range

2.3.4 Impact of mental health conditions on outcomes in patients with atrial fibrillation

People with severe MHCs have a life expectancy reduced by approximately 10 years when compared with the general population, mainly due to increased somatic morbidity (Nordentoft et al., 2013; Plana-Ripoll et al., 2019; E. R. Walker et al., 2015). Cardiovascular diseases are the most common contributor to the elevated mortality rates observed in patients with MHCs, accounting for approximately one-fifth of lost life-years (Jayatilleke et al., 2017). Cardiovascular risk factors, such as diabetes and metabolic syndrome, prevail among patients with MHCs (Laursen et al., 2007; Osborn et al., 2008; Suvisaari et al., 2016). However, their somatic comorbidities are often underrecognized (D. J. Smith et al., 2013). Moreover, undertreatment of recognized cardiovascular risk factors further predisposes these patients to poor outcomes (Hamieh et al., 2021).

Conflicting evidence regarding the association between MHCs and adverse outcomes in patients with AF has been provided by a few cohort studies. The main findings of these studies are summarized in **Table 3**. Overall, while the reported crude outcomes have generally been worse for patients with MHCs than for those without, the observed independent associations between MHCs and outcomes have been somewhat inconsistent. Schauer et al. first reported an association between any MHC and increased risk of stroke, intracranial haemorrhage and gastrointestinal bleeding in patients receiving warfarin between 1997 and 2002 in the United States (Schauer et al., 2005). Baumgartner et al. observed that anxiety disorder, but not depression, was independently associated with an increased combined risk of ischemic stroke and intracranial haemorrhage in AF patients newly started on warfarin (Baumgartner et al., 2018). However, they found no significant association between depression or anxiety and ischemic stroke or intracranial haemorrhage separately. Paradise et al. demonstrated only a slightly increased risk of major haemorrhage in AF patients with any MHC receiving warfarin, whereas no specific MHC alone was associated with increased bleeding (Paradise et al., 2014). Dodson et al. reported an association between depression and traumatic intracranial bleeding(Dodson et al., 2016). Moreover, Søgaard et al. reported outcomes among patients with incident AF treated for severe MHCs in a hospital setting, irrespective of whether they received OAC or not (Søgaard et al., 2017). In this study, the rate of ischemic stroke or major bleeding did not differ between patients with severe depression, bipolar disease or schizophrenia compared to matched controls, whereas the rate of fatal thromboembolism was higher for patients with schizophrenia than for matched controls, but not for patients with severe depression or bipolar disorder.

The impact of MHCs on outcomes has also been evaluated in two meta-analyses. A meta-analysis pooling the associations of all MHC categories with ischemic stroke and bleeding outcomes found that the presence of any MHC was associated with a

25% higher risk of ischemic stroke and a 12% higher risk of major bleeding (Teppo et al., 2021). Another meta-analysis focusing only on severe mental disorders—that is, psychotic disorders and bipolar disorder—found no significant association between severe mental disorders and ischemic stroke or bleeding outcomes (Farran et al., 2022). Interestingly, in patients without AF, several meta-analyses have reported that different MHCs increase the risk of ischemic stroke (Dong et al., 2012; Li et al., 2014; Yuan et al., 2021).

The existing literature has several important shortcomings. The outcome studies published to date utilize varying and mostly compressed or incomplete definitions of MHCs and outcome events. With the exception of the work by Søgaard et al., all prior outcome studies included only patients already receiving warfarin therapy and thus deemed suitable recipients of OAC treatment. While the authors included comprehensive categories of specific MHCs and outcome variables, they were limited by the exclusion of patients treated outside the hospital system and the lack of data on the quality of OAC therapy. Considering the limitations of these studies and the discrepancies in their findings, more information is required on whether different MHCs increase the risk of adverse outcomes in patients with AF.

Table 3. Characteristics of studies reporting the impact of mental health conditions on the outcome of patients with atrial fibrillation (Modified from Teppo et al. 2021).

Study	Country	Study design	No. of patients	Study interval	MHC	Outcome	Adjusted hazard ratio
Dodson et al. 2017	USA	Retrospective cohort study	31,951	2001–2012	Depression	Traumatic ICH	1.30 (1.05–1.61)*
Baumgartner et al. 2018	USA	Retrospective cohort Study	25,570	2004–2007	Anxiety	Ischemic stroke	1.59 (0.95–2.65)
						ICH	1.63 (0.85–3.12)
						ECH	1.17 (0.80–1.72)
						Ischemic stroke and ICH	1.54 (0.99–2.38)
					Depression	Ischemic stroke	0.96 (0.65–1.41)
						ICH	1.32 (0.84–2.06)
						ECH	0.99 (0.78–1.27)
						Ischemic stroke and ICH	1.08 (0.78–1.49)
Paradise et al. 2014	USA	Retrospective cohort study	103,897	2007–2008	Any MHC	Major haemorrhage	1.19 (1.11–1.27)*
					Anxiety disorder		1.10 (0.98–1.25)
					Bipolar disorder		1.09 (0.89–1.33)
					Depression		1.12 (0.98–1.27)
					PTSD		0.98 (0.86–1.13)
					Schizophrenia		0.81 (0.59–1.13)
					Other psychotic disorders		1.24 (1.02–1.50)*
					GAF >50		1.00 (0.90–1.12)
					Psychiatric hospitalization		1.12 (0.88–1.43)
Schauer et al. 2005	USA	Retrospective cohort study	9,345	1997–2002	Any MHC	Ischemic stroke	1.36 (1.06–1.74)*
						ICH	1.46 (1.04–2.05)*
						GI bleeding	1.19 (1.03–1.39)*
Søgaard et al. 2017	Denmark	Nationwide retrospective cohort study	253,741	2000–2015	Schizophrenia	Ischemic stroke	1.16 (0.72–1.87)
						Fatal TE	2.88 (1.57–5.28)*
						Major bleeding	1.22 (0.87–1.72)
					Severe depression	Ischemic stroke	1.01 (0.64–1.58)
						Fatal TE	0.75 (0.37–1.52)
						Major bleeding	1.00 (0.69–1.45)
					Bipolar disease	Ischemic stroke	0.85 (0.55–1.29)
						Fatal TE	1.23 (0.72–2.09)
						Major bleeding	0.72 (0.51–1.02)

* $p < 0.05$

Abbreviations: ECH, extracranial haemorrhage; GI, gastrointestinal; ICH, intracranial haemorrhage; MHC, mental health condition; GAF, global assessment of functioning. PTSD, post-traumatic stress disorder; TE, thromboembolism

3 Aims

1. To assess whether the initiation of OAC therapy differs between AF patients with and without MHCs (I)
2. To evaluate whether adherence to NOAC therapy in patients with AF is affected by the presence of MHCs (II and III)
3. To investigate whether rhythm control therapies for AF are used less often for patients with MHCs than for those without MHCs (IV)
4. To examine the associations between MHCs and the risk of ischemic stroke, bleeding and death in patients with AF (V and VI)

4 Materials and Methods

4.1 Study population

The Finnish Anticoagulation in Atrial Fibrillation (FinACAF) study (ClinicalTrials identifier: NCT04645537; European Network of Centres for Pharmacoepidemiology and Pharmacovigilance identifier: EUPAS29845) is a retrospective nationwide registry-based cohort study comprising all patients recorded with a diagnosis of AF during 2004–2018 in Finland. Patients were identified from all available national healthcare registers (hospitalizations and outpatient specialist visits: Care Register for Health Care; primary healthcare: Register of Primary Health Care Visits; and the National Reimbursement Register upheld by the Social Insurance Institute).

The inclusion criterion for the registry was an ICD-10 (International Classification of Diseases, 10th revision) diagnosis code I48 (including both AF and atrial flutter) recorded at any time during 2004–2018 in any of the aforementioned registries. Altogether, 411,387 patients with AF were identified.

The current study focused only on those patients who had incident AF; that is, they were diagnosed with AF for the first time during the study period. Thus, patients with a recorded AF diagnosis or a warfarin prescription fulfilled during 2004–2006 were excluded, as these patients had too little recorded medical history to exclude a diagnosis of AF before the study's inception. Additionally, patients with OAC purchases in the year before the index date were excluded, as most of them likely had a prior diagnosis of AF. Patients emigrating during the observation period were also excluded. Thereafter, patients were selected for the study samples according to the aims of the separate studies. The process of selecting patients with incident AF is summarized in **Figure 1**.

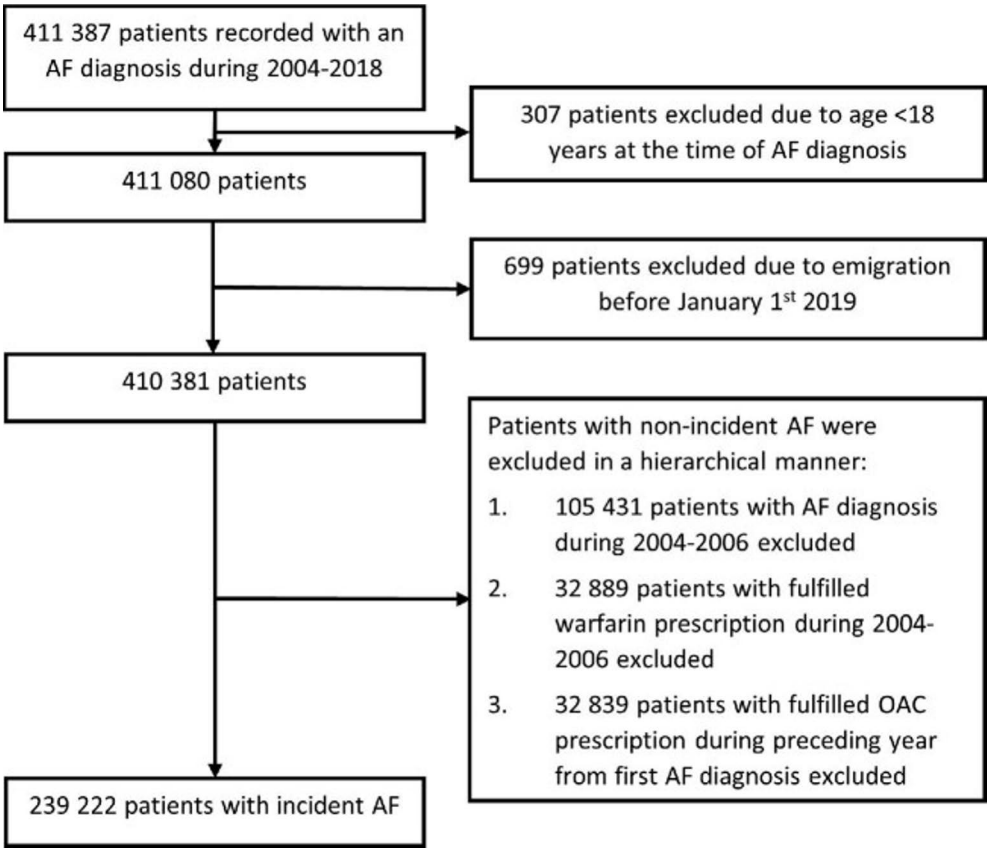

Figure 1. Flowchart of the patient selection process.

4.2 Study ethics

The study protocol was approved by the Ethics Committee of the Medical Faculty of Helsinki University, Helsinki, Finland (nr. 15/2017) and granted research permission from the Helsinki University Hospital (HUS/46/2018). Respective permissions were obtained from the Finnish register holders (KELA 138/522/2018; THL 2101/5.05.00/2018; Population Register Centre VRK/1291/2019-3; Statistics Finland TK-53-1713-18 / u1281; and Tax Register VH/874/07.01.03/2019). The patients' identification numbers were pseudonymized, and the research group received individualized but unidentifiable data. Informed consent was waived due to the retrospective registry nature of the study. The study conforms to the Declaration of Helsinki as revised in 2013.

4.3 Definitions

4.3.1 Mental health conditions

MHCs of interest were depression, bipolar disorder, anxiety disorder, schizophrenia and any MHC. These conditions were chosen due to their high prevalence in the ageing population of patients with AF (GBD 2019 Mental Disorders Collaborators, 2022). Patients were classified into diagnostic groups if they were recorded with the ICD-10 diagnosis code or International Classification of Primary Care, Second Edition (ICPC-2) entry of the condition before the index date as follows: depression (ICD-10: F32, F33, F34.1; ICPC-2: P76), anxiety disorder (ICD-10: F40-F42, F43.1; ICPC-2: P74), bipolar disorder (ICD-10: F31; ICPC-2: P73), schizophrenia (ICD-10: F20; ICPC-2: P72). Patients with more than one of these conditions were classified into each diagnostic category separately. In part of the studies (I, III, IV and V), patients were also classified as having any MHC if they had any of these four aforementioned MHCs or if they had redeemed a prescription of an antidepressant, antipsychotic or mood stabilizing medication within the year before the index date. Patients without these conditions or redeemed psychotropic medications were classified as having no MHC (Anatomical Therapeutic Chemical codes: N05A, N05BE01, N06A). In Study VI, only patients with diagnosed MHCs were classified as having any MHC, and in Study II, the any MHC category was not used.

4.3.2 Baseline characteristics of the study cohort

The comorbidities and socioeconomic data of the cohort patients were obtained from the following linked national registries: Care Register for Health Care (HILMO); Register of Primary Health Care Visits (AvoHILMO); National Reimbursement Register upheld by the Social Insurance Institute (KELA); Finnish Cancer Registry; and National Tax Register. The baseline characteristics of the study cohort were gathered from 2004 until cohort entry, that is, until the first recorded diagnosis of AF.

4.3.3 Outcomes of interest

In Study I, the outcome was the initiation of OAC therapy, which was considered to occur on the date of the first fulfilled OAC (warfarin, apixaban, dabigatran, edoxaban or rivaroxaban) prescription after the cohort entry.

In Study II, the commonly used MPR metric was used to quantify NOAC therapy implementation. The MPR of each patient was calculated by dividing the number of

days covered with the sum of purchased daily doses during persistent therapy by the number of days between the first and the last NOAC purchase dates, added to the days covered with the dose of the last purchase.

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

In Study III, persistence to NOACs was assessed in a time-to-event manner by calculating the time between NOAC initiation and discontinuation, that is, the time between the first and last NOAC purchase before a discontinuation event. A discontinuation event was defined as the first >120-day period without NOAC purchases. In Finland, it is possible to purchase drugs with reimbursement for a maximum of 90 days, and an additional grace period of 30 days was allowed in this study.

In Study IV, the primary outcome was the use of any antiarrhythmic therapy (AAT), including cardioversion, catheter ablation and fulfilled AAD prescription. Additionally, the rates of cardioversion, ablation and AAD use were assessed individually.

In Study V, the outcomes were the first-ever diagnosed ischemic stroke and death. The occurrence of ischemic stroke events was obtained from both primary and hospital care registers and dates of death were obtained from the National Death Register. Finally, in Study VI, we assessed the incidence of adverse bleeding events, including gastrointestinal bleeding and intracranial bleeding, as well as a composite outcome of any bleeding. Bleeding events were obtained only from the hospital care register to ensure that the bleeding event was truly major and clinically relevant.

4.4 Statistical analysis

The chi-square test was used to examine differences between proportions, the independent samples t-test was used to compare normally distributed continuous variables, and the Kruskal–Wallis test was used to compare non-normally distributed continuous variables. Poisson regression was used to estimate incidence rates as well as unadjusted and adjusted incidence rate ratios (IRRs) for treatment and outcome events in patients with and without MHCs. Additionally, because in the ageing population of patients with AF, observation of an event may be hindered by mortality occurring during the study period, competing risk analyses using the Fine-Gray subdistribution hazards regression model with all-cause death as a competing event were performed to estimate the unadjusted and adjusted subdistribution hazard ratios (SHRs) for outcomes. In Study II, unadjusted and adjusted odds ratios (ORs) of

adherent NOAC use were calculated using binary logistic regression. In Study VI, Cox proportional hazards regression was used to determine the unadjusted and adjusted hazard ratios for bleeding events in patients with and without MHCs. In these analyses, the regressions were fitted with a time-varying variable of OAC exposure. The Cox regression model was chosen instead of the Fine-Gray regression in these analyses, since the use of internal time-varying covariates is not recommended in the Fine-Gray regression model (Austin et al., 2020). Additionally, in Study IV, propensity score matching was performed to obtain study cohorts with and without MHCs balanced for baseline variables. The propensity score was estimated with any MHC as the dependent variable using a non-parsimonious logistic regression model that included baseline variables. One-to-one propensity score matching was performed using a calliper width of 0.2, the standard deviation of the logit. Standardized differences <0.10 were considered an acceptable imbalance between the matched cohorts. Statistical analyses were performed with IBM SPSS Statistics software (version 27.0, SPSS, Inc., Chicago, Illinois), R (version 4.0.5, https://www.R-project.org), and Stata (version 15.1, StataCorp LLC, Texas, USA).

5 Results

5.1 Initiation of OAC therapy (I)

Study I investigated the initiation of OAC therapy in patients with and without MHCs. In total, 239,222 patients with incident AF during 2007–2018 were identified with a mean age of 72.7 years (standard deviation (SD) 13.2 years), and the prevalence of any MHC was 19.9%. Patients with MHCs were more often female and had cardiovascular comorbidities, dementia and alcohol use disorder more often than patients with no history of MHCs (**Table 4**). Of note, both patients with and without MHCs had on average high stroke risk scores, with higher scores among patients with MHCs (median CHA_2DS_2-VASc score 4 vs. 3). Similar differences in the baseline characteristics between patients with and without MHCs were observed in all substudies of this dissertation. Patients with any MHC were less likely to initiate OACs during follow-up than patients without MHCs (64.9% vs. 73.3%, $p < 0.001$). After adjustments, depression, bipolar disorder, anxiety disorder, schizophrenia and any MHC were all independently associated with approximately 15% lower cumulative incidence of OAC initiation. While overall OAC coverage markedly increased during the observation period, patients with MHCs were consistently less likely to initiate OACs than patients with no MHC (**Figure 2**). The association with any MHC and a lower OAC initiation rate also persisted during the NOAC era after 2014 (adjusted SHR 0.91, 95% CI 0.89–0.93). The share of NOACs increased over the observation period, and by 2018, OAC therapy was initiated with NOACs in 89.9% of patients with MHCs and 92.4% of patients without MHCs.

Table 4. Baseline characteristics of patients with incident AF.

	No MHC n=191,675	Any MHC n=47,547	Depression n=10,920	Bipolar disorder n=1,129	Anxiety disorder n=4,382	Schizophrenia n=1,560
Age, years (SD)	72.6 (13.0)	72.8 (14.2)	69.8 (14.4)	64.2 (13.0)	66.2 (16.3)	69.6 (11.7)
Female sex	90,754 (47.3)	28 292 (59.5)	6 494 (59.5)	523 (46.3)	2 675 (61.0)	823 (52.8)
Hypertension	147,803 (77.1)	38 637 (81.3)	8 944 (81.9)	892 (79.0)	3 570 (81.5)	1 079 (69.2)
Dyslipidaemia	91,867 (47.9)	23,854 (50.2)	5,688 (52.1)	574 (50.8)	2,136 (48.7)	600 (38.5)
Heart failure	31,886 (16.6)	9,810 (20.6)	2,050 (18.8)	186 (16.5)	702 (16.0)	471 (30.2)
Diabetes	40,143 (20.9)	11,733 (24.7)	2,962 (27.1)	360 (31.9)	1,005 (22.9)	559 (35.8)
Prior stroke	27,463 (14.3)	8,605 (18.1)	1,938 (17.7)	196 (17.4)	693 (15.8)	231 (14.8)
Vascular disease	48,815 (25.5)	13,598 (28.6)	3,057 (28.0)	241 (21.3)	1,058 (24.1)	341 (21.9)
Renal failure	3,816 (2.0)	1,197 (2.5)	319 (2.9)	32 (2.8)	117 (2.7)	34 (2.2)
Liver cirrhosis	911 (0.5)	383 (0.8)	132 (1.2)	16 (1.4)	52 (1.2)	10 (0.6)
Alcohol use disorder	5,081 (2.7)	4,354 (9.2)	1,856 (17.0)	311 (27.5)	746 (17.0)	153 (9.8)
Prior bleeding	20,625 (10.8)	7,055 (14.8)	1,874 (17.2)	185 (16.4)	740 (16.9)	228 (14.6)
Dementia	10,576 (5.5)	7,335 (15.4)	1,480 (13.6)	91 (8.1)	416 (9.5)	187 (12.0)
CHA_2DS_2-VASc score	3 [2–5]	4 [2–5]	4 [2–5]	3 [2–4]	3 [2–5]	3 [2–5]
Modified HAS-BLED score	2 [1–2]	2 [1–3]	2 [1–3]	2 [1–3]	2 [1–3]	2 [1–2]

Values are presented as absolute number (percentage), mean (standard deviation) or median [interquartile range]. Abbreviations: CHA_2DS_2-VASc, congestive heart failure, hypertension, age ≥75 years, diabetes, history of stroke, vascular disease, age 65-74 years, sex category (female); Modified HAS-BLED, hypertension, abnormal renal function or liver enzymes, prior stroke, bleeding history, elderly, drugs or alcohol (without labile INR), INR, international normalized ratio; MHC, mental health condition; SD, standard deviation.

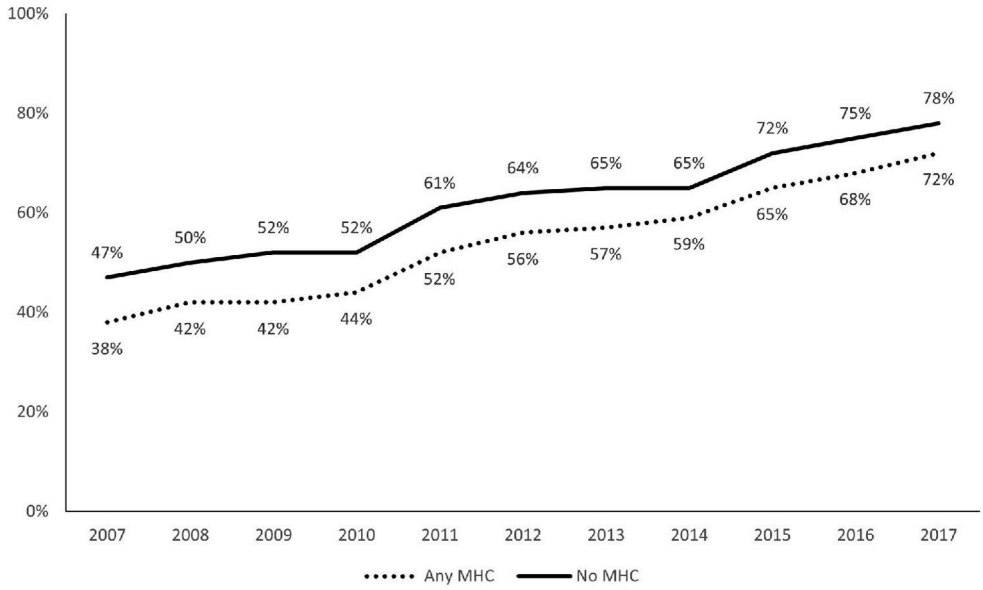

Figure 2. Proportion of patients initiated with OACs within a one-year follow-up according to the year of AF diagnosis.

5.2 Implementation of NOAC therapy (II)

In Study II, we evaluated adherence in the implementation phase of NOAC therapy among patients with newly diagnosed AF. In total, 74,222 patients initiating NOAC therapy with at least two redeemed prescriptions were identified. The mean duration of NOAC therapy during follow-up was 1.7 years (SD 1.4). The mean MPR was 0.84 (SD 0.22), and 59.5% of patients were considered adherent to NOACs, with an MPR ≥0.90. When the analyses covered all NOAC purchases, the mean MPR in patients with depression or bipolar disorder did not differ from those with no history of MHCs, while the MPR was higher in patients with anxiety disorders or schizophrenia. Similarly, the proportion of adherent patients with MPR ≥0.90 was higher in patients with anxiety disorder or schizophrenia and lower in patients using psychiatric medication. However, after adjustments, depression, bipolar disorder and use of psychiatric medications were associated with a lower likelihood of adherent NOAC use, while anxiety disorder and schizophrenia had no effect on NOAC adherence. However, when only persistent drug use was covered in the analyses, anxiety disorder was associated with slightly better NOAC adherence, but the other MHC categories had no impact on NOAC adherence **(Table 5).**

Table 5. Adherence to NOAC therapy.

Clinical condition	Mean MPR	Adherent patients (MPR≥0.90)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
All NOAC purchases				
No MHC	0.843	60.0%	(Reference)	(Reference)
Depression	0.841	59.5%	0.97 (0.91–1.04)	0.92 (0.84–0.99)
Bipolar disorder	0.857	60.1%	0.99 (0.80–1.22)	0.77 (0.61–0.97)
Anxiety disorder	0.857*	63.8%*	1.17 (1.05–1.31)	1.08 (0.96–1.21)
Schizophrenia	0.879*	67.9%*	1.38 (1.11–1.72)	1.13 (0.90–1.43)
Psychiatric medication	0.836*	57.8%*	0.90 (0.86–0.94)	0.94 (0.90–0.99)
Persistent NOAC use				
No MHC	0.888	67.7%	(Reference)	(Reference)
Depression	0.889	67.9%	1.01 (0.94–1.08)	0.97 (0.90–1.05)
Bipolar disorder	0.902	69.2%	1.08 (0.87–1.35)	0.80 (0.63–1.02)
Anxiety disorder	0.906*	71.8%*	1.23 (1.10–1.38)	1.18 (1.04–1.34)
Schizophrenia	0.920*	74.7%*	1.41 (1.11–1.78)	1.14 (0.90–1.47)
Psychiatric medication	0.880*	65.0%*	0.89 (0.85–0.93)	0.98 (0.94–1.04)

Abbreviations: CI, confidence interval; MHC, mental health condition; MPR, medication possession ratio; OR, odds ratio. *p<0.05. Adjustments were made for age, sex and calendar year of NOAC initiation, heart failure, hypertension, diabetes, prior stroke, vascular disease, prior bleeding, alcohol abuse, renal failure and liver cirrhosis or failure, dementia, income, NOAC dosing, prior use of VKAs and polypharmacy.

5.3 Persistence of NOAC therapy (III)

Study III assessed the persistence of NOAC use in patients with incident AF. Altogether, 67,503 patients with incident AF with an indication of permanent anticoagulation (females with CHA_2DS_2-VASc score >2 and males with CHA_2DS_2-VASc score >1) starting NOACs were identified. Overall, 22.1% of patients were observed to discontinue NOAC therapy during follow-up. Persistence to NOACs decreased considerably over time, especially in individuals with MHCs (**Figure 3**). After adjusting for confounding factors, when compared to patients without MHCs, a higher rate of therapy discontinuation was observed in all MHC groups: adjusted SHRs (95% CI) for any MHC 1.16 (1.11–1.21), depression 1.32 (1.22–1.42), bipolar disorder 1.44 (1.15–1.80), anxiety disorder 1.25 (1.11–1.41), and schizophrenia 1.30 (1.02–1.64). Similar findings were observed in patients with only a single specific MHC, apart from patients with only anxiety disorders without other MHCs, in whom a higher risk of nonpersistence to NOACs was not observed. Additionally, after discontinuing NOAC therapy, patients with MHCs were less likely to restart OAC therapy, either with NOACs or VKA, than patients without MHCs (73.1% vs. 76.2%, $p < 0.001$).

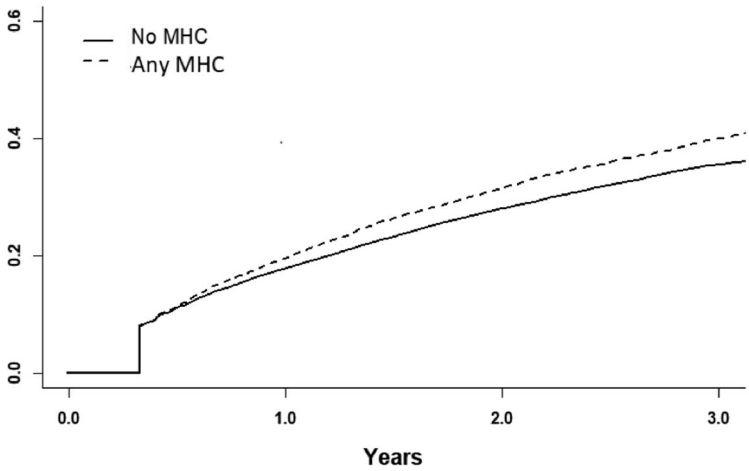

Figure 3. Cumulative incidence curve of NOAC nonpersistence in patients with and without MHCs.

5.4 Use of rhythm control therapies (IV)

In Study IV, which assessed the use of rhythm control therapies, 239,222 patients with incident AF were identified. The cumulative incidence of any AAT use was lower among patients with MHCs than among those without (**Figure 4)**. Lower use of any AAT, AADs, cardioversion and catheter ablation were observed consistently in all MHC groups (**Table 6)**. However, for patients with depression or bipolar disorder, the use of catheter ablation did not differ significantly from patients without MHCs after controlling for confounding factors. Patients with MHCs were less likely to receive all modalities of rhythm control therapies over the study period.

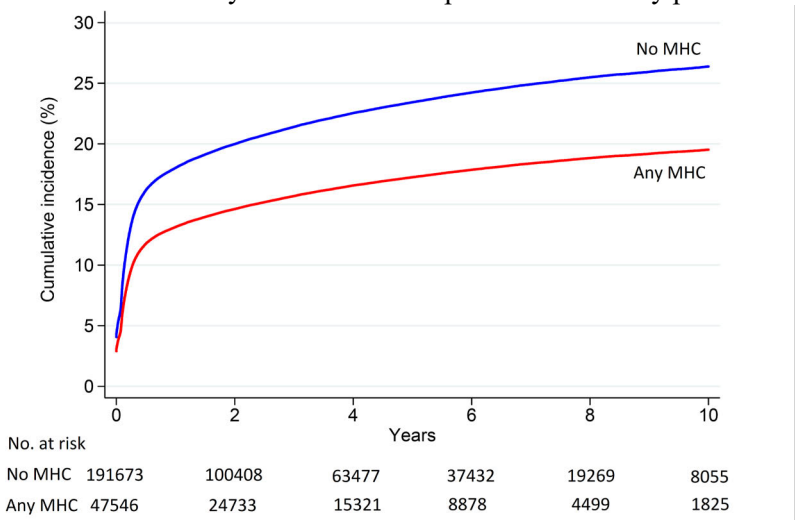

Figure 4. Cumulative ten-year incidence function of the use of any antiarrhythmic therapy.

Table 6. Incidence rate ratios of use of rhythm control therapies according to the presence of MHCs.

Outcome	Clinical condition	Unadjusted IRR	Adjusted IRR
Any AAT	No MHC	(Reference)	(Reference)
	Any MHC	0.748 (0.731–0.766)	0.811 (0.791–0.831)
	Depression	0.880 (0.841–0.922)	0.805 (0.768–0.844)
	Bipolar disorder	0.875 (0.764–1.001)	0.730 (0.637–0.835)
	Anxiety disorder	0.964 (0.899–1.034)	0.706 (0.658–0.757)
	Schizophrenia	0.451 (0.382–0.534)	0.408 (0.345–0.482)
AADs	No MHC	(Reference)	(Reference)
	Any MHC	0.852 (0.822–0.883)	0.889 (0.857–0.923)
	Depression	0.967 (0.901–1.038)	0.911 (0.848–0.979)
	Bipolar disorder	0.876 (0.706–1.086)	0.780 (0.628–0.969)
	Anxiety disorder	1.076 (0.968–1.197)	0.832 (0.747–0.926)
	Schizophrenia	0.447 (0.339–0.590)	0.423 (0.320–0.558)
Cardioversion	No MHC	(Reference)	(Reference)
	Any MHC	0.727 (0.707–0.748)	0.794 (0.772–0.817)
	Depression	0.878 (0.833–0.926)	0.797 (0.755–0.842)
	Bipolar disorder	0.896 (0.768–1.046)	0.744 (0.637–0.869)
	Anxiety disorder	0.900 (0.829–0.978)	0.663 (0.610–0.721)
	Schizophrenia	0.438 (0.358–0.535)	0.391 (0.320–0.477)
Catheter ablation	No MHC	(Reference)	(Reference)
	Any MHC	0.811 (0.752–0.874)	0.837 (0.775–0.904)
	Depression	1.114 (0.972–1.277)	0.904 (0.787–1.040)
	Bipolar disorder	0.911 (0.587–1.413)	0.660 (0.425–1.027)
	Anxiety disorder	1.051 (0.842–1.311)	0.564 (0.451–0.705)
	Schizophrenia	0.238 (0.107–0.531)	0.215 (0.097–0.480)

Abbreviations: AAD, antiarrhythmic drug; AAT, antiarrhythmic therapy; IRR, incidence rate ratio; MHC, mental health condition. 95% confidence intervals in parentheses. IRRs are estimated by Poisson regression and adjusted for age, sex, calendar year of AF diagnosis, dementia, alcohol use disorder, vascular disease and heart failure. Any AAT includes use of AADs, cardioversion and catheter ablation.

5.5 Risk of ischemic stroke and mortality (V)

Study V determined the rates of first-ever ischemic stroke and death in patients with and without MHCs. Altogether, 203,154 patients with incident AF without a history of stroke or TIA were identified. During follow-up, patients with any MHC were more likely to experience ischemic stroke and death than patients with no history of MHCs (8.9% vs. 7.8% and 37.6% vs. 29.7%, respectively; both $p < 0.01$) (**Figure 5**). After propensity score matching, any MHC was associated with a higher risk of

ischemic stroke, while no association was observed between the other MHC categories and stroke risk. However, after further adjusting the regressions for OAC use during follow-up, none of the MHC categories were associated with the risk of ischemic stroke. Any MHC, depression and schizophrenia were associated with higher mortality even after propensity score matching and adjusting for differences in OAC use (**Table 7**).

Table 7. Risk estimates of ischemic stroke and mortality for MHCs after propensity score matching.

Clinical condition	Ischemic stroke SHR	Mortality HR
Model 1		
No MHC	(Reference)	(Reference)
Any MHC	1.054 (1.005–1.106)	1.210 (1.180–1.242)
Depression	0.970 (0.865–1.086)	1.245 (1.172–1.324)
Bipolar disorder	1.403 (0.951–2.068)	1.085 (0.886–1.327)
Anxiety disorder	0.885 (0.725–1.081)	1.100 (0.987–1.226)
Schizophrenia	0.947 (0.709–1.264)	1.671 (1.465–1.905)
Model 2 (adjusted for OAC use)		
No MHC	(Reference)	(Reference)
Any MHC	1.033 (0.985–1.085)	1.149 (1.116–1.175)
Depression	0.961 (0.857–1.077)	1.208 (1.136–1.283)
Bipolar disorder	1.398 (0.947–2.006)	1.068 (0.873–1.308)
Anxiety disorder	0.878 (0.718–1.034)	1.059 (0.950–1.181)
Schizophrenia	0.803 (0.594–1.085)	1.543 (1.352–1.761)

Abbreviations: HR, hazard ratio; MHC, mental health condition; SHR, subdistribution hazard ratio. Model 1 without adjustments, Model 2 adjusted for OAC initiation during follow-up (before stroke). SHRs estimated with Fine-Gray subdistribution regression with all-cause death as a competing event, and HRs estimated with Cox proportional hazards regression. 95% confidence intervals in parentheses.

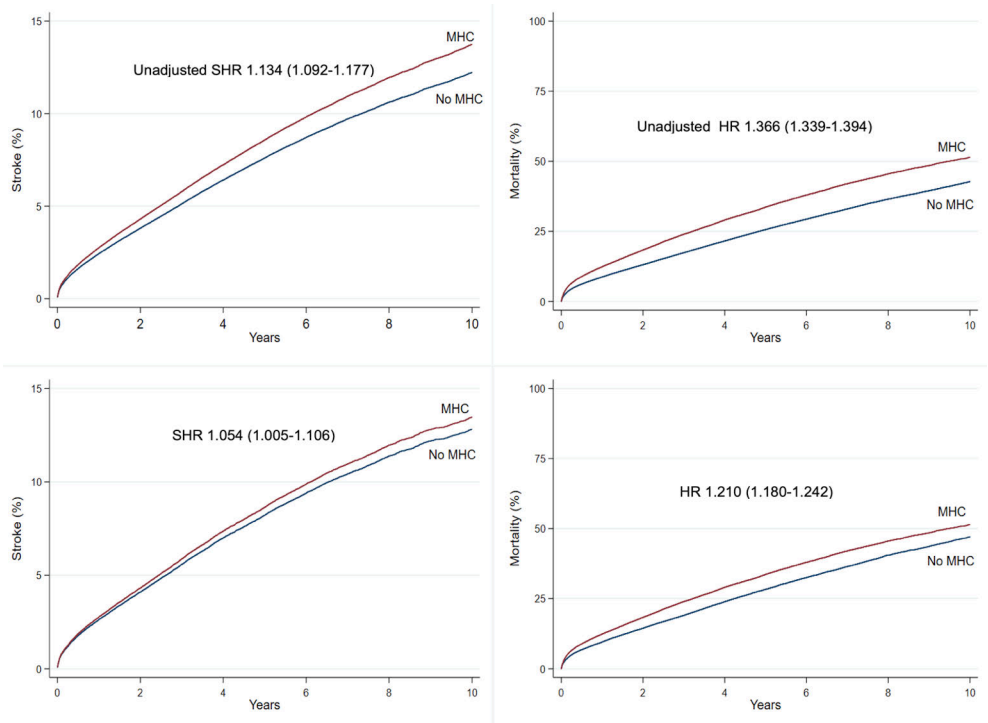

Figure 5. Cumulative incidence curves of first-ever ischemic stroke (left) and all-cause death (right) before (upper panel) and after (lower panel) propensity score matching in patients with and without any MHC.

5.6 Risk of bleeding (VI)

Study VI focused on the risk of adverse bleeding events in patients with AF and MHCs. A total of 205,109 patients with incident AF without bleeding events prior to AF diagnosis were identified, and the incidence rate of first-ever any bleeding was 3.06 (95% CI 3.03–3.10) per 100 patient-years.

The unadjusted hazards of gastrointestinal (GI), intracranial (IC) and any bleeding events were higher among patients with any diagnosed MHC or depression when compared to patients without MHCs (**Figure 6)**. Likewise, the crude GI bleeding hazard was higher in patients with anxiety disorders. Otherwise, the unadjusted bleeding rates were similar in patients with and without MHCs (**Table 8)**.

In the adjusted analyses, any MHC and depression were associated with all bleeding categories. Additionally, anxiety disorder was associated with a higher risk of GI bleeding. However, bipolar disorder or schizophrenia were not associated with a higher risk of bleeding (**Table 8)**. The bleeding risks associated with MHCs were similar among men and women, as well as among patients under and over 65 years old. OAC use was independently associated with the hazard of any bleeding (adjusted

HR 1.24 (95% CI 1.21–1.28)), and this association did not differ between patients with and without MHCs (interaction term: OAC exposure x any MHC, adjusted HR 1.05 (95% CI 0.97–1.13), p = 0.25). Exposure to serotonin reuptake inhibitors was not associated with the risk of any bleeding (adjusted HR 0.97 (95% CI 0.86–1.10)).

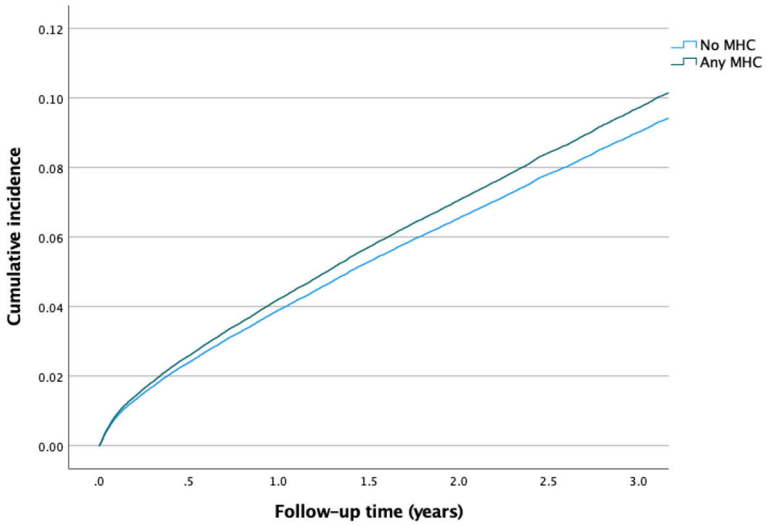

Figure 6. Crude cumulative incidence curve of any bleeding according to the presence of any MHC.

Table 8. Hazard ratios of bleeding according to the presence of MHCs.

	Any bleeding		GI bleeding		IC bleeding	
Clinical condition	**Unadjusted HR**	**Adjusted HR**	**Unadjusted HR**	**Adjusted HR**	**Unadjusted HR**	**Adjusted HR**
No MHC	(Reference)	(Reference)	(Reference)	(Reference)	(Reference)	(Reference)
Any MHC	1.09 (1.03-1.15)	1.19 (1.12-1.27)	1.25 (1.14-1.36)	1.19 (1.08-1.32)	1.17 (1.05-1.31)	1.19 (1.05-1.34)
Depression	1.14 (1.07-1.22)	1.21 (1.13-1.30)	1.32 (1.19-1.46)	1.22 (1.09-1.37)	1.22 (1.08-1.39)	1.18 (1.02-1.36)
Bipolar disorder	0.96 (0.79-1.18)	1.10 (0.90-1.35)	0.96 (0.78-1.36)	0.95 (0.67-1.35)	1.12 (0.76-1.64)	1.27 (0.86-1.88)
Anxiety disorder	1.01 (0.91-1.13)	1.21 (1.08-1.35)	1.26 (1.07-1.49)	1.31 (1.10-1.56)	0.99 (0.80-1.25)	1.11 (0.87-1.39)
Schizophrenia	0.91 (0.76-1.10)	0.99 (0.82-1.20)	1.03 (0.76-1.40)	0.97 (0.71-1.31)	1.15 (0.82-1.63)	1.22 (0.86-1.74)

Abbreviations: GI, gastrointestinal; HR, hazard ratio; IC, intracranial; MHC, mental health condition. 95% confidence intervals in parentheses. HRs estimated by Cox regression and adjusted for age, gender, cohort entry year, dementia, cancer, alcohol use disorder, prior stroke, abnormal liver function, abnormal kidney function, diabetes, hypertension, any vascular disease, heart failure and income quartiles and use of serotonin reuptake inhibitors and oral anticoagulants.

6 Discussion

6.1 Use of OAC therapy (I, II and III)

Studies I, II and III focused on the initiation of OACs and the implementation and persistence of NOAC therapy in patients with and without MHCs. MHCs appeared common in patients with AF, with an overall prevalence of 20% in the study cohort. The studies demonstrated that these patients were less likely to initiate stroke prevention with OACs. However, in the implementation phase of NOAC therapy, medication adherence was materially similar between patients with and without MHCs. Persistence to NOACs was lower in patients with MHCs; that is, patients with MHCs discontinued their NOAC therapy at a higher rate than patients with no history of MHCs. Moreover, after discontinuing NOAC therapy, patients with MHCs were less likely to restart OAC therapy, either with NOAC or VKA. The overall utilization of OAC therapy for stroke prevention is therefore substantially lower in patients with MHCs than in those without MHCs. This is an alarming finding, especially because, according to the stroke risk scores, patients with MHCs are actually at higher risk of ischemic stroke.

After adjustments, any MHC was associated with a 17% lower rate of OAC initiation. This finding is in concordance with previous studies reporting lower use of stroke prevention among patients with AF suffering from mental disorders (Fenger-Grøn et al., 2020, 2021; Teppo et al., 2021). These results are also in line with prior studies reporting that patients with psychiatric disorders are often undertreated for their somatic comorbidities (Druss et al., 2000; Redelmeier et al., 1998). The data from most previous studies on OAC use for these patients are derived from the first decade of the 2000s, and study I adds to prior evidence by showing that disparities in OAC initiation have not reduced significantly since the introduction of easier-to-use NOACs (Teppo et al., 2021). An MHC-related deficit in OAC use is also observed, despite the improved understanding of the importance of AF as a stroke risk factor and the publication of new clinical practice guidelines for the management of AF (Hindricks et al., 2021). Importantly, previous studies have lacked primary care data, which has limited the generalizability of their results considerably in relation to the current work, which uniquely covers patients from all levels of care.

While patients with MHCs seemed to have poorer implementation of NOAC therapy when all NOAC purchases were included in the analysis, a clinically meaningful difference was no longer observed when only persistent drug use was included. Thus, during persistent drug use, implementation of NOACs seems materially similar between patients with and without MHCs. This finding is somewhat discordant with the previous literature. Although no previous studies have assessed the specific relationship between MHCs and NOAC adherence in patients with AF, several studies have reported poor implementation of medical therapies for other chronic conditions for patients with MHCs (Holvast et al., 2019; Levin et al., 2016; May et al., 2010; Phan, 2016). Nonetheless, in line with our results, few reports of non-inferior therapy implementation among patients with MHCs can be found in previous literature (Foley et al., 2021; Hamieh et al., 2021). Publication bias may also partly explain the lack of previous literature with "null results," in concordance with our results of similar medication adherence in patients with and without MHCs.

Previous literature on the persistence of NOAC use in patients with MHCs and AF is lacking, as is research on the implementation of NOAC therapy. However, our observation of the lower persistence of NOAC therapy is in concordance with the abovementioned suboptimal treatment implementation and persistence of other disorders among patients with MHCs (Gajria et al., 2014; Holvast et al., 2019; Levin et al., 2016; Phan, 2016). Moreover, the one-year NOAC persistence rates of 77–79% observed in Study III are comparable with the results of a recent multinational study reporting an average one-year NOAC persistence of 82% (Komen, Pottegård, et al., 2021).

The observed disparities in OAC use are likely multifactorial. A higher prevalence of contraindications for OAC therapy has been reported in patients with MHCs than in those not afflicted by these conditions (G. A. Walker et al., 2011). Excessive alcohol consumption prevalence among patients with MHCs has raised concerns, since it has been linked with poor control of warfarin therapy and a higher risk of falls and major bleeding (Dodson et al., 2016; Efird et al., 2013; Jaakkola et al., 2017; Rose et al., 2010). The higher prevalence of other comorbidities in patients with MHCs may influence clinical decision making regarding OAC therapy. However, clear disparities in OAC initiation were observed even after comprehensive adjustment for bleeding risk factors and other comorbidities.

Concerns regarding the safe use of OACs owing to insufficient self-care resources and medication adherence in patients with MHCs may prevent physicians from prescribing OACs (Chapman & Horne, 2013; Hwang et al., 2014). However, as demonstrated in Study II, the implementation of NOAC therapy is not meaningfully affected by the presence of MHCs, and an unfounded preconception of unsafe drug use by these patients should not lead to withholding vital stroke prevention treatment. Nonetheless, such prejudices towards patients with MHCs

have been shown to bias physicians in their clinical decision making (Lawrence & Kisely, 2010).

The social and cognitive challenges sometimes associated with MHCs may also impair communication between patients and healthcare professionals, affecting shared decision making. These difficulties in communication may also hamper patients' understanding of the importance of OAC therapy, as well as its lifelong nature, possibly contributing to the observed lower therapy persistence. Likewise, the poor economic conditions prevalent in this patient group may impair optimal stroke prevention with OACs, particularly regarding NOACs, which are considerably more expensive than VKA, even though 42–65% of the costs of NOACs have been reimbursed to AF patients at risk of stroke in Finland since 2012. That said, VKA would enable inexpensive and efficient stroke prevention for low-income patients. Patients with MHCs face barriers to the treatment of their somatic comorbidities owing to the separation of somatic and psychiatric healthcare, poorer health literacy, low socioeconomic conditions and inadequate self-care resources (Hwang et al., 2014). These barriers to treatment likely impair follow-up of OAC therapy, and treatment discontinuation may therefore go unnoticed more easily.

These same factors do not seem to affect initiation, implementation or persistence of stroke prevention with OACs to the same extent, since meaningful disparities in the implementation phase of NOAC therapy were not observed, whereas clear MHC-related deficits were observed in treatment initiation and persistence. Disparities in the initiation of OAC therapy may be more related to individual-level treatment decisions, whereas the deficits in adherence may reflect more deficiencies in the healthcare system and its challenges in providing integrated care with adequate follow-up for these vulnerable patients. Furthermore, the impact of the abovementioned factors on OAC use most likely differs between specific MHCs; that is, the reasons for withholding OAC therapy or treatment discontinuation may be different in patients with anxiety disorders or schizophrenia.

6.2 Use of rhythm control therapies (IV)

In Study IV, a profound disparity in the use of rhythm control therapies was observed between patients with and without MHCs. An MHC-related deficit was observed in the use of all AAT modalities, including AADs, cardioversion and catheter ablation. Lower use of AAT modalities was also observed in all MHC categories, even though the disparities in the use of catheter ablation did not reach statistical significance in patients with depression or bipolar disorder. These treatment disparities were observed throughout the observation period from 2007 to 2018.

Although prior studies specifically assessing the use of rhythm control therapies in patients with AF and MHCs are lacking, findings in concordance with Study IV

can be found in the existing literature. Previous studies have reported lower use of cardiovascular procedures among patients with mental disorders experiencing myocardial infarction (Druss et al., 2000). Likewise, the lower initiation of OAC therapy in patients with MHCs observed in previous studies and in Study I are in accordance with the lower use of rhythm control therapies (Teppo et al., 2021). Patients with schizophrenia had the lowest rates of AAT use, less than half the rates of patients without MHCs, a finding that corresponds with previous reports on the high rates of undertreatment of medical comorbidities in patients with schizophrenia (Fleetwood et al., 2021).

The factors underlying the lower use of AATs in these patients are most likely similar to the reasons behind lower OAC use, as discussed in Section 6.1. In addition, AADs have clinically meaningful interactions with antidepressants and antipsychotics, limiting their use among patients with MHCs (Trujillo & Nolan, 2000).

The previous literature also includes findings that suggest a possible increase in the use of rhythm control therapies in patients with MHCs. Depression and anxiety have been shown to increase visits to medical care for AF management and AF-related symptoms, which might support a higher rate of symptomatic treatment attempts. Likewise, depression and anxiety have been associated with a higher risk of AF recurrence after catheter ablation (Yu et al., 2012), potentially leading to repeat procedures. Alcohol abuse, which is associated with MHCs in the current study sample, has been reported to increase AF paroxysms, total AF burden and AF recurrence after ablation and cardioversion procedures (Kuppahally et al., 2009; Qiao et al., 2015; Takigawa et al., 2016; Voskoboinik et al., 2016, 2020).

Importantly, since the data used lacked actual patient-level reasons for withholding AATs for patients with MHCs, it was not possible to definitively distinguish whether the observed MHC-related deficit in AAT use actually represents undertreatment of this patient group or clinically well-founded reticence in the use of potentially harmful therapies.

6.3 Outcomes (V and VI)

Studies V and VI demonstrated that MHCs are individually associated with a higher risk of bleeding and death but not with the risk of ischemic stroke in patients with incident AF. Regarding specific MHCs, higher all-cause mortality was associated with depression and schizophrenia. When compared to patients without MHC, a more than 50% higher adjusted mortality rate was observed in patients with schizophrenia, which corresponds with previous reports of poor overall survival in these patients (Hayes et al., 2017; Keinänen et al., 2018). Anxiety and bipolar disorders were not independently associated with a higher risk of death. Depression

and anxiety disorders were associated with bleeding events, whereas a similar association was not observed with bipolar disorder and schizophrenia. The associations with outcomes varied between specific MHCs, suggesting differences between MHCs in the underlying mechanisms predisposing patients to bleeding, ischemic stroke and mortality.

In Study V, an association between MHCs and ischemic stroke was observed before adjusting for the initiation of OAC therapy, but a significant association was no longer observed after adjustment. Likewise, adjusting for OAC initiation attenuated the risk estimates of all-cause mortality for MHCs. Hence, the observed disparity in OAC use seems to partly explain the higher crude ischemic stroke and mortality rates in patients with MHCs. According to the interaction analyses in Study VI, the bleeding risks associated with OAC therapy were similar for patients with and without MHCs, suggesting that OAC therapy can be used for stroke prevention for patients with AF, regardless of the presence of MHCs. Hence ,with regard to bleeding risks and the safety of OAC therapy, there seems to be no clinical grounds for poorer OAC coverage for patients with MHCs.

The finding of similar ischemic stroke risk between AF patients with and without MHCs is in line with the recent Danish cohort study, but in contrast with the pooled results of a recent meta-analysis that reported a higher ischemic stroke risk associated with MHCs (Søgaard et al., 2017; Teppo et al., 2021). Several meta-analyses have reported an association between MHCs and ischemic stroke, regardless of the presence of AF, but our study did not confirm these findings in patients with AF (Li et al., 2014; Pan et al., 2011; Pérez-Piñar et al., 2017; Yuan et al., 2021). Most previous studies have been subject to major information, confounding and selection biases owing to selected and small patient populations, use of only hospital-level data, lack of data on confounding factors and heterogeneity in the definitions of MHCs. Therefore, the results of the current study provide substantially more robust evidence on this matter. Moreover, the findings highlight that the outcome disparities between patients with and without MHCs can be attenuated with the appropriate use of OAC therapy for stroke prevention.

MHCs, particularly depression and anxiety disorders, were associated with a higher risk of bleeding. Whether these observed bleeding risks are a result of residual confounding effects or the direct impact of MHCs cannot be definitively distinguished from the available registry-based data, and the observed associations are most likely multifactorial. Undertreatment and underdiagnosis of cardiovascular comorbidities in patients with MHCs are likely also reflected in their higher bleeding risk (de Hert et al., 2011; Desai et al., 2002). Unhealthy lifestyle habits, such as tobacco use, are also common in patients with mental disorders, and although the data used covered diagnosed alcohol use disorders, patients with MHCs may have higher alcohol consumption below the threshold of clinical diagnosis (Jakobsen et

al., 2018; Lasser et al., 2000). Importantly, the risk of bleeding was higher among patients with MHCs, despite adjusting for an extensive set of patient characteristics, including several known bleeding risk factors. Hence, the bleeding risks associated with these MHCs are not fully captured by commonly used bleeding risk stratification tools. This emphasizes the importance of appropriate bleeding risk assessment and the management of modifiable bleeding risk factors in this vulnerable patient group.

6.4 Strengths and limitations

The results of the current study must be interpreted with consideration of several limitations inherent in retrospective cohort studies based on administrative registry data. Most importantly, the observed findings represent associations and not necessarily causation between MHCs, treatments and outcomes. Information and confounding biases may affect the results owing to unmeasured, missing or inappropriately recorded data in the healthcare registries. The reliability of administrative data for research purposes is dependent on the accuracy of documentation of the medical records by healthcare professionals and is therefore prone to human errors. Patients with AF were identified by an observed I48 ICD-10 diagnosis code, and therefore, some of these patients have actually had atrial flutter. Data on AF subclassifications were also lacking.

Importantly, the definitions of MHCs as a single group and individually (depression, bipolar disorder, anxiety disorder and schizophrenia) used in this work are simplifications of complex real-world mental disorders. Due to the nature of the data, condition severity or changes in mental health occurring during the study period could not be accounted for. Patients with any MHC were assessed categorically as a single group, as many similar challenges and barriers in healthcare are experienced by patients within the wide spectrum of mental health conditions. Moreover, as a common limitation of registry-based studies, lifestyle-related factors, such as tobacco use and exercise habits, were missing in our data, except for the recorded alcohol use disorder diagnoses. Likewise, we lacked data on body weight and obesity, which may particularly impact the results regarding the use of rhythm control therapies. Residual confounding by unmeasured factors cannot be excluded and is especially likely in the outcome analyses of Studies V and VI. Studies I and IV lacked socioeconomic data, but these data were linked to the dataset for Studies II, III, V and VI, and the results of these studies were adjusted for patients' income levels.

The initiation and use of OACs and AADs were based on pharmacy claims data, and we therefore lacked information on whether patients actually took these medicines. Likewise, we lacked data on the medications used during

hospitalizations, which may affect our results. Hence, the adherence measures and the OAC exposure variables used are only approximations of the real-life drug use. Furthermore, it was not possible to distinguish whether the lower OAC initiation rate was due to lower prescribing of OAC or whether patients with MHCs did not claim their prescribed drugs. The data used lacked information on the actual reasons for withholding OAC therapy or rhythm control therapies, and the lack of data on symptom burden is an important limitation in Study IV. Hence, the observed MHC-related deficit in treatment does not necessarily reflect solely a lower quality of care, but is likely a result of several factors, some of which are not captured by the available data. Moreover, the observed MHC-related deficits may, at least in part, also reflect clinically well-founded decisions in the management of AF. Finally, whether our findings can be generalized to other countries with different healthcare systems is unknown.

Notwithstanding the limitations of administrative data, the nationwide data used in the current study has some clear strengths in relation to the research questions of this dissertation. By linking the Finnish national registries from both specialist care and primary healthcare, as well as from the National Reimbursement Register upheld by the Social Insurance Institute, the FinACAF study population uniquely covers practically all patients diagnosed with AF in Finland from all levels of care (Lehto, Halminen, et al., 2022). The FinACAF cohort is the only nationwide study sample of all AF patients, including primary care data. The hospital care and causes of death registers used are well validated for research purposes and have shown relatively high diagnostic accuracy, especially regarding cardiovascular diseases (Leppälä et al., 1999; Sund, 2012; Tolonen et al., 2007). Furthermore, studies conducted in other Nordic countries, with comparable healthcare system registers, have demonstrated high accuracy in identifying patients with AF from registered diagnosis codes when compared to information obtained by electrocardiogram review (Rix et al., 2012; J. G. Smith et al., 2010). The data used covers all OAC and AAD purchases, since these drugs are not sold over the counter without prescription in Finland. The administrative data has virtually no loss to follow-up, apart from due to marginal emigration, and the patients can therefore be followed up for long periods. Thus, the large nationwide coverage of the available data enables the assessment of real-life health inequities in treatment, as well as in outcomes. Owing to the large sample size and comprehensive data on comorbidities and other patient characteristics, the results of this thesis could be adjusted for multiple confounding factors to obtain considerably more solid evidence on the associations between MHCs and outcomes than prior studies in this field.

6.5 Future implications

The most important findings of the current study are the poorer OAC coverage and lower use of rhythm control therapies among patients with AF and MHCs than among those without a history of MHC. To improve the treatment of this fragile patient group, it is important to increase awareness of these deficits in their treatment. Increasing OAC use and adherence to OACs among patients with MHCs would likely improve their outcomes and deserves further research. Importantly, the observed differences in the treatment and outcomes of AF may represent only a tip of the iceberg in the overall health disparities faced by patients with MHCs. Whether similar inequalities exist in the treatment and outcomes of other somatic disorders requires investigation. Moreover, it is vital to further assess the mechanisms underlying these treatment shortfalls and to explore effective interventions to reduce these disparities. More in-depth integration of somatic and psychiatric healthcare systems would likely reduce barriers to somatic healthcare for individuals with mental disorders. Regular evaluation of somatic health status and ongoing medical therapies could improve treatment of somatic comorbidities, medication adherence and outcomes in this patient group, particularly among those with severe mental disorders, also regardless of the presence of AF. Furthermore, enhanced social support might benefit the somatic treatment of patients with severe MHCs. Holistic patient-centred approaches and continuity in patient care are likely key elements in achieving optimal and long-lasting medical treatment for this vulnerable patient group. Finally, policymakers should focus on reducing the health disparities faced by patients with MHCs.

7 Conclusions

In patients with AF, those with MHCs are less likely to initiate OACs and more likely to discontinue NOAC therapy than patients without MHC. Interventions to improve stroke prevention in patients with AF and MHCs are needed (Studies I and III).

The implementation of NOAC therapy is similar in AF patients with and without MHCs. Therefore, unfounded preconceptions of unsafe drug use in patients with MHCs should not result in withholding vital stroke prevention treatment (Study II).

Patients with MHCs are less likely to receive rhythm control therapies for AF than patients without a history of MHC, suggesting possible shortfalls in the symptomatic treatment of AF in patients with MHCs (Study IV).

Patients with AF and MHCs have an overall worse prognosis than patients without MHCs in terms of crude ischemic stroke, bleeding and mortality rates. MHCs are independently associated with higher risk of mortality and bleeding, but not with the risk of ischemic stroke. Appropriate use of OAC therapy could improve outcomes in patients with MHCs. In addition, a comprehensive bleeding risk assessment appears important in this vulnerable patient population (Studies V and VI).

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