



Anticoagulation for atrial fibrillation in people with serious mental illness in the general hospital setting

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ABSTRACT

Objective: People with serious mental illnesses (SMI) have an increased risk of stroke compared to the general population. This study aims to evaluate oral anticoagulation prescription trends in atrial fibrillation (AF) patients with and without a comorbid SMI.

Methods: An open-source retrieval system for clinical data (CogStack) was used to identify a cohort of AF patients with SMI who ever had an inpatient admission to King's College Hospital from 2011 to 2020. A Natural Language Processing pipeline was used to calculate CHA2DS2-VASc and HASBLED risk scores from Electronic Health Records free text. Antithrombotic prescriptions of warfarin and Direct acting oral anti-coagulants (DOACs) (apixaban, rivaroxaban, dabigatran, edoxaban) were extracted from discharge summaries.

Results: Among patients included in the study ($n = 16\ 916$), 2.7% had a recorded co-morbid SMI diagnosis. Compared to non-SMI patients, those with SMI had significantly higher CHA2DS2-VASc (mean (SD): 5.3 (1.96) vs 4.7 (2.08), $p < 0.001$) and HASBLED scores (mean (SD): 3.2 (1.27) vs 2.5 (1.29), $p < 0.001$). Among AF patients having a CHA2DS2-VASc ≥ 2 , those with co-morbid SMI were less likely than non-SMI patients to be prescribed an OAC (44% vs 54%, $p < 0.001$). However, there was no evidence of a significant difference between the two groups since 2019.

Conclusion: Over recent years, DOAC prescription rates have increased among AF patients with SMI in acute hospitals. More research is needed to confirm whether the introduction of DOACs has reduced OAC treatment gaps in people with serious mental illness and to assess whether the use of DOACs has improved health outcomes in this population.

1. Introduction

People suffering from serious mental illnesses (SMI) such as schizophrenia, bipolar disorder and severe depression have a high prevalence of cardiovascular diseases, contributing to 10–20 years of potential life lost (Walker et al., 2015). Atrial fibrillation (AF) is the most prevalent sustained cardiac arrhythmia and is associated with a fivefold increased

risk of stroke (Kirchhof et al., 2016). According to the National Institute for Health and Care Excellence (NICE) guidelines, the management of the thromboembolic risk of AF requires a comprehensive assessment of risk factors for thromboembolic (using the CHA2AD2-VASc tool) and bleeding events (using ORBIT or HAS-BLED tools), and long-term treatment with oral anticoagulants when appropriate (Linden, 2014; Lip et al., 2010; Rutherford et al., 2018).

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Anticoagulation in AF patients is achieved by the prescription of either a vitamin K antagonist (VKA) (eg warfarin) or one of the direct oral anticoagulants (DOACs) (dabigatran, rivaroxaban, apixaban or edoxaban) (Jones et al., 2014). Warfarin and other vitamin K antagonists were the only class of oral anticoagulants available up until 2009, when DOACs were developed. DOACs have a different mechanism of action inhibiting thrombin or activated factor X (factor Xa) and are now considered leading therapeutic alternatives to warfarin (Jones et al., 2014; Ruff et al., 2014). They offer several advantages over vitamin K antagonists, such as not having a narrow therapeutic window requiring frequent International Normalised Ratio (INR) monitoring and dose adjustments, a rapid onset and offset of action, and absence of dietary limitations, making them potentially more suitable for many people with a diagnosis of SMI (Ruff et al., 2014).

Although oral anticoagulation has been effective in reducing the risk of stroke in people with AF, underuse has been sustainably reported, especially in patients with co-morbid SMI (Fenger-Grøn et al., 2021; Jaakkola et al., 2021; Schmitt et al., 2015; Walker et al., 2011). The anticoagulation treatment deficit in people with SMI may be attributed to challenges in self-management and adhering to treatment regimens, drug-drug interactions, bleeding concerns and factors that increase bleeding risk, social deprivation as well as fragmented medical care (Kennedy et al., 2013; Lawrence and Kisely, 2010; Platt et al., 2008).

People with AF and co-morbid SMI are at increased risk of not receiving oral anticoagulation (Teppo et al., 2021), but to date, little is known of whether this has changed since the introduction of DOACs. This study aims to evaluate anticoagulation prescription trends in a large inner-city hospital, King's College Hospital (KCH), over the past 10 years in people with both AF and comorbid SMI who met the CHA2DS2-VASc criteria for anticoagulation treatment.

2. Methods

2.1. Cohort selection

We used CogStack, an open-source information retrieval platform for clinical data (Jackson et al., 2018), to identify a cohort of adult patients who ever had an inpatient admission to KCH in the time between 2011-01-01 to 2020-08-01 and in whom AF had been documented in the discharge summary.

The discharge summaries were searched for the exact keywords “AFib”, “AF”, “PAF” or “Atrial Fibrillation” using our previously validated search strategy (Bean et al., 2019). Patients who were directly discharged from the clinical decision unit or the emergency department were eligible for inclusion in the cohort as they did not have discharge summaries.

We then employed a search strategy in that cohort to identify the presence or absence of any SMI diagnosis recorded anywhere in the clinical records between 2011-01-01 to 2020-08-01. The search algorithm was adapted from our previously published risk scoring algorithm (Bean et al., 2019) to detect the following SMI diagnoses: bipolar disorder, schizophrenia, severe depression, psychosis, delusional disorder or mania, while excluding dementia and conditions secondary to an organic problem or substance use. The risk score pipeline was used to map these general concepts to any specific child term in the Systemized Nomenclature of Medicine – Clinical Terms (SNOMED CT) ontology (El-Sappagh et al., 2018). If any of these terms was detected and not negated it was considered an SMI diagnosis. We used MedCAT (Kraljevic et al., 2021) as the underlying NLP tool to detect mentions of any of these conditions in discharge summaries or clinical notes for the AF patient cohort.

2.2. CHA2DS2-VASc and HASBLED risk scores calculation

To calculate CHA2DS2-VASc and HASBLED risk scores, we used the Natural Language Processing (NLP) pipeline developed by Bean et al.

(2019), that allows calculation of the risk scores from Electronic Health Records (EHR) free text, again, anywhere in the clinical notes within the previously defined timeframe. We used MedCAT (Kraljevic et al., 2021) as the underlying NLP tool for clinical concept annotation and the SNOMED CT ontology for terminology mapping of clinical concepts.

2.3. Oral anticoagulant prescriptions

Antithrombotic prescriptions of oral anticoagulants (OACs) (apixaban, rivaroxaban, dabigatran, edoxaban, warfarin) were extracted from free text discharge summaries within the previously defined timeframe. This was performed using a custom NLP pipeline validated in a previous work (Bean et al., 2019).

2.4. Statistical analysis

Categorical variables were presented as counts and percentages and compared using a Chi-squared test, whereas continuous variables were presented as means and standard deviations and compared using Student *t*-test. All statistical analyses were performed in Python using numpy and statsmodels. A $P < 0.05$ after Bonferroni correction for multiple testing was considered significant. In analysis of prescribing trends, SMI status and OAC prescribing were determined per admission (i.e. individual patients can move from the “non-SMI” to “SMI” category if their SMI diagnosis was not known for earlier admissions). In overall statistics, patients were considered at their last admission to hospital.

Ethical approval

This project was conducted under London South East Research Ethics Committee approval (reference 18/LO/2048) granted to the King's Electronic Records Research Interface (KERRI), project ID 20200201.

3. Results

3.1. Cohort identification

Based on the search strategy described above, we identified 21 546 patients with mentions of AF. After excluding patients based on the admission date, death, and age (<18), we ended up with a cohort of 16 916 adult patients admitted to KCH with a diagnosis of AF, of whom 465 (2.7%) had a recorded comorbid SMI diagnosis. Among AF patients with SMI, 199 were prescribed an oral anticoagulant (Fig. 1). Table 1 shows the characteristics of the study cohort. Overall, patients with SMI were younger and had higher rates of other comorbidities than those without SMI.

3.2. CHA2DS2-VASc and HASBLED scores

Fig. 2 shows the distribution of AF patients across the various CHA2DS2-VASc and HASBLED scores by mental health status. Compared to non-SMI patients, those with SMI had significantly higher CHA2DS2-VASc (mean (SD): 5.3 (1.96) vs 4.7 (2.08), $p < 0.001$) and HASBLED scores (mean (SD): 3.2 (1.27) vs 2.5 (1.29), $p < 0.001$). Among the SMI patients, 96% had a CHA2DS2-VASc ≥ 2 and 73% had a HASBLED score ≥ 3 whereas among non-SMI patients the proportions were 93% and 51% respectively.

3.3. OAC prescription trends

Overall, 54% of AF patients with a CHA2DS2-VASc ≥ 2 were prescribed an OAC. When stratified by mental health status, a significant difference in overall OAC prescription rate was detected between SMI and non-SMI patients (44% vs 54% respectively, $p < 0.001$). In particular, warfarin was prescribed twice as often to non-SMI than SMI patients ($p < 0.001$) whereas no significant difference in the prescription of

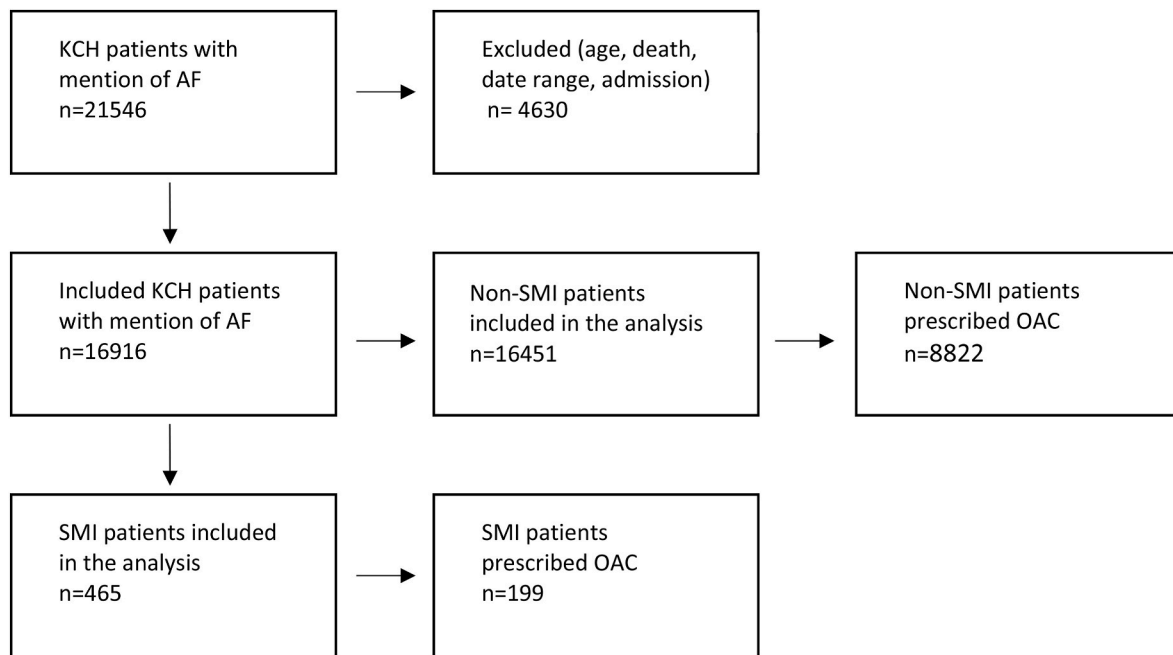


Fig. 1. Cohort selection.

Table 1
Characteristics of study cohort.

Group	Factor	All AF Patients (N = 16916)	SMI (N = 465)	Not SMI (16451)	P-value
Demographics	Age	75.61 (12.99)	71.88 (13.92)	75.72 (12.95)	<0.001
	Male	9443 (55.8%)	259 (55.7%)	9184 (55.8%)	1.0
CHA2DS2-VASc Components	vascular disease	6120 (36.2%)	214 (46.0%)	5906 (35.9%)	<0.001
	Age 65–74	3846 (22.7%)	122 (26.2%)	3724 (22.6%)	1.0
	stroke	8637 (51.1%)	312 (67.1%)	8325 (50.6%)	<0.001
	hypertension	12981 (76.7%)	385 (82.8%)	12596 (76.6%)	0.085
	Female	7473 (44.2%)	206 (44.3%)	7267 (44.2%)	1.0
	congestive heart failure	5862 (34.7%)	210 (45.2%)	5652 (34.4%)	<0.001
	diabetes mellitus	6146 (36.3%)	234 (50.3%)	5912 (35.9%)	<0.001
HAS-BLED Components	Age ≥ 75	10053 (59.4%)	230 (49.5%)	9823 (59.7%)	<0.001
	alcohol	740 (4.4%)	72 (15.5%)	668 (4.1%)	<0.001
	bleeding	9856 (58.3%)	352 (75.7%)	9504 (57.8%)	<0.001
	drugs increasing bleed risk	659 (3.9%)	21 (4.5%)	638 (3.9%)	1.0
	abnormal renal function	7873 (46.5%)	301 (64.7%)	7572 (46.0%)	<0.001
	uncontrolled hypertension	0 (0.0%)	0 (0.0%)	0 (0.0%)	1.0
	stroke	8637 (51.1%)	312 (67.1%)	8325 (50.6%)	<0.001
HAS-BLED Score	abnormal liver function	1696 (10.0%)	83 (17.8%)	1613 (9.8%)	<0.001
	0	883 (5.2%)	11 (2.4%)	872 (5.3%)	0.28
	1	2960 (17.5%)	37 (8.0%)	2923 (17.8%)	<0.001
	2	4430 (26.2%)	80 (17.2%)	4350 (26.4%)	<0.001
	3	4419 (26.1%)	144 (31.0%)	4275 (26.0%)	0.75
	4	3249 (19.2%)	123 (26.5%)	3126 (19.0%)	<0.01
	5	862 (5.1%)	64 (13.8%)	798 (4.9%)	<0.001
CHA2DS2-Vasc Score	6	107 (0.6%)	6 (1.3%)	101 (0.6%)	1.0
	7	6 (0.0%)	0 (0.0%)	6 (0.0%)	1.0
	total	2.55 (1.3)	3.18 (1.27)	2.53 (1.29)	<0.001
	0	381 (2.3%)	6 (1.3%)	375 (2.3%)	1.0
	1	778 (4.6%)	11 (2.4%)	767 (4.7%)	1.0
	2	1468 (8.7%)	24 (5.2%)	1444 (8.8%)	0.33
	3	2232 (13.2%)	43 (9.2%)	2189 (13.3%)	0.54
	4	2789 (16.5%)	72 (15.5%)	2717 (16.5%)	1.0
	5	2866 (16.9%)	85 (18.3%)	2781 (16.9%)	1.0
	6	2774 (16.4%)	91 (19.6%)	2683 (16.3%)	1.0
Anticoagulation Status	7	2123 (12.6%)	72 (15.5%)	2051 (12.5%)	1.0
	8	1138 (6.7%)	45 (9.7%)	1093 (6.6%)	0.54
	9	367 (2.2%)	16 (3.4%)	351 (2.1%)	1.0
	Total	4.72 (2.08)	5.28 (1.96)	4.72 (2.08)	<0.001
	Any OAC	9021 (53.3%)	199 (42.8%)	8822 (53.6%)	<0.001
	Warfarin	4086 (24.2%)	56 (12.0%)	4030 (24.5%)	<0.001
	DOAC	4935 (29.2%)	143 (30.8%)	4792 (29.1%)	1.0

Note: Age is shown as mean (SD) and tested with a t-test, all other values are N (%) and tested with a chi-squared test.

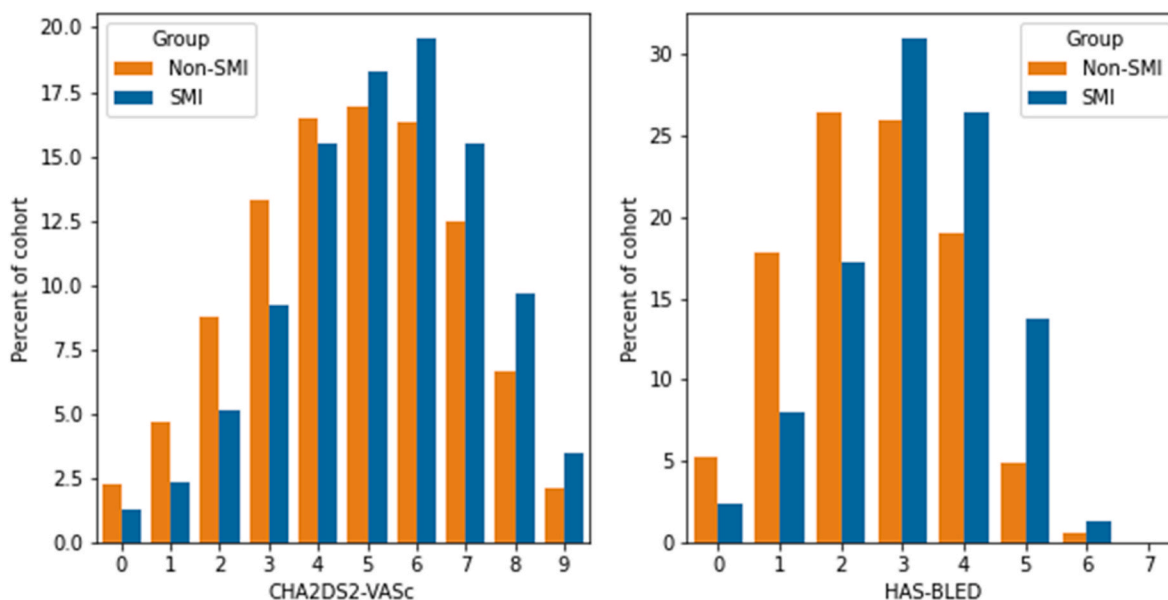


Fig. 2. CHA2DS2-VASc and HASBLED scores for the entire AF cohort (SMI and non-SMI) at their most recent hospital admission.

DOAC was detected between the two groups ($p = 1.0$) (Table 2).

Although there was a significant difference in anticoagulation rates between AF patients with and without SMI in the overall cohort, the trend over time indicated that the overall average was not representative of current clinical practice (Fig. 3a). We therefore split the cohort chronologically into visits before and after January 2019 and analysed the rates separately (Table 2). Although the proportion of AF patients with HASBLED ≥ 3 was consistently higher in the SMI group (77% vs 61%, $p < 0.001$), from 2019 onwards there was no longer evidence of a significant difference in overall anticoagulation rates between AF

patients with and without co-morbid SMI having a CHA2DS2-VASc ≥ 2 (56% vs 63%, $p = 0.35$) (Table 2). In the non-SMI group, the proportion of patients with a CHA2DS2-VASc ≥ 2 prescribed any OAC significantly increased between the two timepoints (51%–63%, $p < 0.001$) as did the proportion of patients at high risk of bleeding (52%–61%, $p < 0.001$).

We also split OAC prescribing in each group into warfarin vs DOAC use, finding qualitatively similar trends in both patient groups, with Warfarin use decreasing and DOAC use increasing over time (Fig. 3b). DOAC prescribing rates now exceed warfarin rates in both groups.

4. Discussion

This study provides insights on the oral anticoagulation (warfarin vs DOACs) prescription rate among AF patients with and without a co-morbid SMI using electronic health records. Compared to non-SMI patients, those with SMI had more comorbidities and significantly higher CHA2DS2-VASc and HASBLED scores. Among AF patients having CHA2DS2-VASc ≥ 2 , those with co-morbid SMI were less likely than non-SMI patients to be prescribed any OAC, particularly warfarin (but not DOACs). However, there was no evidence of a significant difference between the two groups since 2019.

Our findings are in line with previous research showing that there is a treatment gap between SMI and non SMI patients (Fenger-Grøn et al., 2021; Jaakkola et al., 2021; Schmitt et al., 2015). Using the Veterans Health Administration database ($n = 12\ 190$), Schmitt et al. (2015) reported that warfarin eligible patients with psychotic disorders ($n = 122$) were less likely to receive the treatment compared to controls (AOR 0.77; 95% CI, 0.65–0.90). A nationwide cohort study in Finland ($n = 239\ 222$) reported that diagnoses of bipolar disorder ($n = 1129$) (adjusted subdistribution hazard ratio (aSHR): 0.838; 95% CI 0.824 to 0.852) and schizophrenia ($n = 1560$) (aSHR 0.838; 95% CI 0.824 to 0.851) were associated with lower rates of oral anticoagulation therapy in AF patients after adjusting for multiple confounders (age, sex, stroke, and bleeding risk factors) (Jaakkola et al., 2021). Similarly, using a Danish nationwide cohort ($n = 147\ 810$), Fenger-Grøn et al. (2021) reported that among newly AF diagnosed patients, bipolar disorder ($n = 1208$) and schizophrenia ($n = 572$) were associated with a significantly lower frequency of oral anticoagulation therapy initiation adjusting for age and sex (bipolar: -12.7% , 95% CI: -15.3% to -10.0% ; schizophrenia: -24.5% 95% CI: -28.3% to -20.7%). Anticoagulation treatment deficit remained significant after the introduction of DOACs

Table 2

Anticoagulation rates for the AF cohort at high risk of stroke, stratified by SMI status and time.

Time	Factor	All AF Patients	SMI	Not SMI	P-value
All	HAS-BLED ≥ 3	8582 (54.5%)	334 (74.6%)	8248 (53.9%)	<0.001
	Any OAC	8506 (54.0%)	195 (43.5%)	8311 (54.3%)	<0.001
	Warfarin	3839 (24.4%)	55 (12.3%)	3784 (24.7%)	<0.001
	DOAC	4667 (29.6%)	140 (31.2%)	4527 (29.6%)	1.0
	N	15757	448	15309	
2019–2020	HAS-BLED ≥ 3	2409 (61.3%)	119 (76.8%)	2290 (60.6%)	<0.001
	Any OAC	2477 (63.0%)	86 (55.5%)	2391 (63.3%)	0.35
	Warfarin	500 (12.7%)	15 (9.7%)	485 (12.8%)	1.0
	DOAC	1977 (50.3%)	71 (45.8%)	1906 (50.5%)	1.0
	N	3932	155	3777	
2011–2018	HAS-BLED ≥ 3	6157 (52.2%)	215 (73.4%)	5942 (51.7%)	<0.001
	Any OAC	6012 (51.0%)	109 (37.2%)	5903 (51.3%)	<0.001
	Warfarin	3334 (28.3%)	40 (13.7%)	3294 (28.6%)	<0.001
	DOAC	2678 (22.7%)	69 (23.5%)	2609 (22.7%)	1.0
	N	11795	293	11502	

Note: only patients with CHA2DS2-VASc ≥ 2 are included. All values are N (%) and tested with a chi-squared test.

a. Trend in anticoagulation rate over time by SMI diagnosis for AF patients at high risk of stroke (CHA2DS2-VASc ≥ 2).

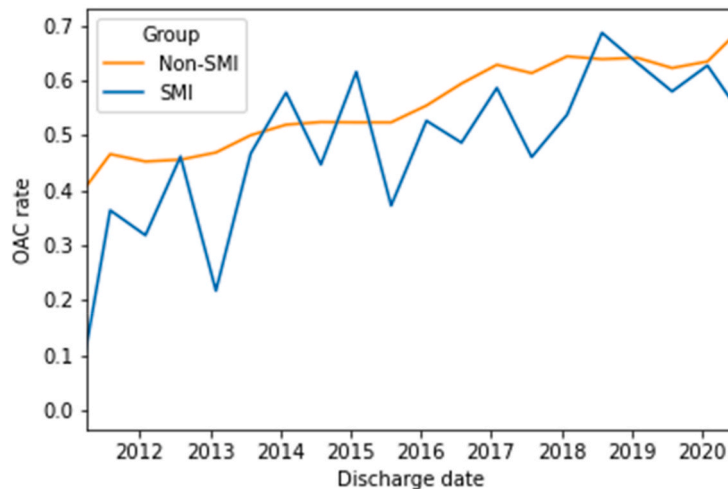


Fig. 3a. Trend in anticoagulation rate over time by SMI diagnosis for AF patients at high risk of stroke (CHA2DS2-VASc ≥ 2). Note: Rates were aggregated on a 6-months level and limited to 2020-06-30 as the last complete six months in the dataset.

b. Trend in anticoagulation rates over time split by SMI diagnosis and type of OAC for AF patients at high risk of stroke (CHA2DS2-VASc ≥ 2).



Fig. 3b. Trend in anticoagulation rates over time split by SMI diagnosis and type of OAC for AF patients at high risk of stroke (CHA2DS2-VASc ≥ 2). Note: Rates were aggregated on a 6-months level and limited to 2020-06-30 as the last complete six months in the dataset. DOAC = direct acting oral anticoagulant.

(analysis performed between 2013 and 2016) among patients with schizophrenia but not among those with bipolar disorder (Fenger-Grøn et al., 2021).

In this study, we report that there was no evidence of a significant difference in anticoagulation prescription rates between SMI and non-SMI AF patients after 2019 suggesting an improvement in anticoagulation therapy among a population considered at high risk of adverse events. However, the prescription rate of any OAC only reached 44% among SMI patients and 54% among non-SMI patients whose CHA2DS2-VASc ≥ 2 . This means that up until 2020, a large proportion of AF patients was not prescribed an OAC despite being at high risk of stroke. Previous studies have attributed OAC treatment deficit to concerns about the increased bleeding risk although no previous research has shown that the benefits of the treatment are offset by this risk (Paradise et al., 2014; Rutherford et al., 2018; Schauer et al., 2005).

Instead, according to NICE guidelines, people with high bleeding risk score should be managed for factors increasing the bleeding risk such as uncontrolled hypertension, alcohol, and relevant medications (Linden, 2014). Our findings suggest that clinicians are adhering to these guidelines as despite higher HASBLED scores, there was an increase in OAC prescription rates among AF patients particularly those with co-morbid SMI.

Labile INR is another issue for people on warfarin. People with mental illness on warfarin spend less time in therapeutic range and have a higher proportion of sub- and supra-therapeutic INR values compared to the general population (Maki et al., 2013; Razouki et al., 2014; Rose et al., 2010). Given the larger therapeutic range and the simpler dosing regimen, DOACs may be better alternatives in people with active features of mental illness (January et al., 2019). This was practically noted in our population as DOAC prescribing rate has shown a substantial

increase over time (2011–2020) while warfarin use has decreased.

Despite being younger, AF patients with SMI had higher stroke and bleeding risks (measured by the CHA₂DS₂-VASc and HASBLED scores) compared to non-SMI patients, mainly due to the higher prevalence and incidence of physical comorbidities (Correll et al., 2017; Lai et al., 2020, 2022). This is in line with previous studies assessing associations and outcomes of atrial fibrillation in patients with mental illness. In a Danish nationwide cohort study, people with schizophrenia had a crude 5-year hazard ratio (HR) of 3.16 (95% CI 1.78 to 5.61) for fatal thromboembolic events, with trends towards increased risks of bleeding (1.37; 95% CI: 0.99 to 1.90) (Søgaard et al., 2017). Similarly, another study reported that patients with psychiatric illness (including schizophrenia, affective psychosis, and other nonorganic psychosis) receiving warfarin had an increased risk of intracranial haemorrhage (adjusted HR 1.5; 95% CI: 1.04, 2.1), gastrointestinal bleeding (adjusted HR 1.2; 95% CI: 1.03, 1.4) and stroke (adjusted HR 1.4; 95% CI: 1.1, 1.7) (Schauer et al., 2005). A recent meta-analysis reported that AF patients with any mental health condition were at 25% higher adjusted ischemic stroke risk (RR 1.25, 95% CI: 1.08–1.45) and 17% higher bleeding risk (RR 1.17, 95% CI: 1.08–1.27) compared to patients without mental illness (Teppo et al., 2021).

Our study has limitations. First, the analysis is based on data extracted from electronic health records using an NLP-based approach. Although the major variables were manually validated in our analysis (accuracy: 96% for AF, 95% for SMI, 80% for CHA₂DS₂-VASc), and MedCAT¹⁸ has been validated in a number of sites for various conditions, it is likely that our automatically extracted variables contain errors. However, the issue of accuracy is not only limited to our approach but is an issue with conventional EHR data, where even in seemingly robust registries data accuracy is not universally high (Faxon and Burgess, 2016; Poulos et al., 2021). Second, the study population was limited to patients admitted to the hospital as they tend to have more accurately recorded data, especially in terms of drug prescription, therefore may not be fully representative of the overall population. Additionally, it was not possible to reliably distinguish whether OAC prescription was from the community or the hospital by searching for data in the discharge summaries as they included information about the medical history and medications prescribed prior to admission. Third, NICE guidelines now recommend ORBIT rather than HASBLED as a bleeding risk assessment tool, however, by the time the new guidelines were released (2021) data extraction and validation were completed. Given that there is little difference in sensitivity and specificity between the two tools we proceeded with HASBLED. Fourth, the co-morbidities captured in this study were restricted to the CHA₂DS₂-VASc and HASBLED components. This approach allowed us to focus on a set of variables for which we could validate our pipeline and are accepted as clinically relevant in this context, but other risk factors associated with increased risk of poor outcomes in AF patients with co-morbid mental illness may not have been recorded. Fifth, rates were aggregated on a 6-months level for the trend analysis with patients contributing only once to the interval (most recent admission within the interval) and more than once to different intervals. Patients with multiple admissions could be a potential cause of bias, however, the risk is low knowing that most patients included in the study had only 1 admission (71% had only 1 admission, 92% had at most 3 admissions and 93% had at most 5 admissions). Finally, this study was conducted over a period of 10 years in one hospital, part of King's Health Partners, an Academic Health Sciences Centre which prioritises mind-body care and awareness of inequities. Although findings of this study may be generalizable, particularly as it covers a large population, further research should be done in other organizations using different electronic health records to validate the data.

In this study, oral anticoagulation prescription rate has shown an increasing trend among both SMI and non-SMI patients with no evidence of a significant difference between the two groups since 2019 in one major London teaching hospital. A substantial rise in DOAC prescription

was noted among all AF patients regardless of their SMI status. AF patients with comorbid mental illness had high stroke and bleeding risks mainly attributed to the increased prevalence and incidence of contributing risk factors. More research is needed to confirm whether the introduction of DOACs has reduced OAC treatment gap between SMI vs non-SMI patients and whether the use of DOACs has improved the health outcomes in people with SMI.

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Declaration of competing interest

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