**EDITORIAL**

**Impact of mental health conditions on anticoagulation prescription in people with atrial fibrillation**

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Word count: 1017

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The association between atrial fibrillation (AF) and stroke is well established. With AF-related strokes being larger and associated with worse outcomes(1), appropriate oral anticoagulant (OAC) prescribing is paramount. However, patients presenting with AF are a heterogeneous group and anticoagulant prescribing practice may vary depending on numerous factors, including comorbidities, socio-demographic characteristics and likelihood of medication adherence. Evidence examining the impact of mental health conditions (MHCs) on OAC prescription is limited.

In this issue of *European Heart Journal: Quality of Care & Clinical Outcomes*, Jaakkola *et al.* present the findings from an analysis of anticoagulant prescribing practice in those with MHCs, from a large (n=239,222) Finnish registry, FinACAF(2). Specifically, the authors examined anxiety disorder, depression, bipolar disorder and schizophrenia. MHCs were prevalent in approximately 1 in 5 patients and were more common in women and those with cardiovascular comorbidities. OAC initiation was significantly lower among those with MHCs compared with controls without MHCs (64.9% vs. 73.3%, *p*<0.001) and for each MHC individually. The associations were attenuated after adjustment for comorbidities and year of cohort entry, but remained significant(2). Median time to OAC initiation was also significantly longer in MHC patients compared with controls (16 vs. 12 days, *p*<0.001). Analyses of propensity score matched patients with and without MHCs to adjust for significant differences in baseline characteristics demonstrated similar findings (cumulative incidence of OAC initiation 57.7% vs. 62.2%). The overall rate of prescription improved over time, from 45.3% in 2007 to 76.8% in 2017, in line with increasing awareness of the importance of anticoagulation, changes to AF guidelines and the introduction of non-vitamin K antagonist OAC (NOACs), however, the prescription rate remained lower in those with MHCs.

The FinACAF study addresses an important gap in our knowledge: whilst there is evidence of under-treatment of cardiovascular disease in those with MHCs(3) – and whilst MHCs are not uncommon amongst the AF population(4,5) – there is little data on anticoagulation prescribing practice in this group in the era of NOACs.

The potential for confounding should be considered in this complex patient group, particularly as there are recognised interactions between cardiovascular and arrhythmia risk, bleeding, mental health, socio-economic status (SES) and stroke risk (Figure 1). For example, it has previously been shown that OAC prescribing rates are worse for those with lower SES(6), which is also a recognised risk factor for poorer mental health(7,8); the present study(2) was not able to adjust for SES. A similar, Danish, study (including over 147,000 patients) of OAC prescribing in MHC patients adjusted for SES and found that OAC prescribing was significantly attenuated after adjustment(9,10). In particular, differences in bipolar disorder were largely explained by SES, though the deficit in OAC prescribing in schizophrenia remained unexplained(10). There are, however, differences between the Danish(9,10) and Finnish(2) studies, including absence of primary care data in the Danish study, differences in NOAC usage, and varying diagnostic codes used to identify MHCs, which limits the ability to compare directly.

A number of factors affect anticoagulant prescribing practice in patients with MHCs. For example, there may be interactions between OACs and psychotropic medications, or contraindications due to bleeding, particularly in those at risk of deliberate self-harm. Many MHCs are associated with impaired cognition, which may affect the patient’s ability to engage with shared decision making and medication adherence, and reduce the likelihood of adhering with monitoring requirements and daily intake of OAC. For example, a retrospective study of 419,952 US patients estimated non-adherence to be as high as 68.2% in MHC patients prescribed anti-psychotics(11). There is also an increased risk of alcohol excess in those with MHCs(12) may affect the patient’s willingness to initiate or adhere to treatment. These factors may impact on physician prescribing practice, either due to perceived increased bleeding risk or doubt over appropriate self-management behaviours and medication adherence required for life-long OAC prescription. These factors may be compounded by healthcare systems which separate psychiatric services from other medical services, as well as difficulties or delays accessing psychiatric care in some countries.

Whilst OAC prescribing rates were demonstrably lower in those with MHCs in the present study, it is also important to assess the impact of this on hard clinical endpoints, such as stroke, bleeding and mortality, in future research. Treatment adherence and quality of INR control (among those receiving vitamin-K antagonists) are important co-factors. These aspects were outside of the scope of this study, however the same author group recently undertook a systematic review and meta-analysis and demonstrated that the presence of MHCs increased the risk of both stroke and major bleeding in AF patients(13). OAC prescribing, as with the present study, was lower in MHC patients, and time-in-the-therapeutic-range (TTR) was also worse. A previous Danish nationwide study (which also demonstrated significantly lower rates of OAC prescription among patients with severe MHCs), found that there was no significant difference in ischaemic stroke risk compared to those without MHCs after adjustment for comorbidities(12). However, other studies have shown an independent association between MHCs and the risk of stroke(14), with depression and anxiety symptoms associated with increased mortality rates among those prescribed OACs(15).

Some of this complex interplay may be explained by the concept of the “heart-brain-axis”, which is increasingly recognised as an important factor in conditions such as Takotsubo cardiomyopathy, peri-partum cardiomyopathy and AF(16). Higher burden of AF has been linked to reduced cognitive function, only partially explained by silent embolic events and micro-haemorrhage, and studies are underway to attempt to understand the underlying mechanisms(16–18). This highlights the multifactorial and convoluted relationship between MHCs, AF, stroke and bleeding; whilst OAC prescribing practice likely plays a role, the full story is significantly more complex (Figure 1).

How, then, should we manage patients with concomitant AF and MHCs? A standardised approach such as the “Atrial Fibrillation Better Care” (ABC) pathway provides physicians with a straightforward, evidenced-based system to manage care for all AF patients. The ABC approach has been shown to lower the risk of adverse outcomes(19), and the “C” component includes psychosocial management, including mental health status. Greater attention needs to be paid to assessment of mental health given the impact on treatment, morbidity and mortality, and quality of life.

**Competing interests**

PC: None to declare

GYHL: Consultant and speaker for BMS/Pfizer, Boehringer Ingelheim and Daiichi-Sankyo. No fees are received personally.

DL: Investigator-initiated educational grants from Bristol Myers Squibb (BMS) and Boehringer Ingelheim; speaker for Boehringer Ingelheim, Bayer, and BMS/Pfizer and consultant for Boehringer Ingelheim, Bayer, BMS/Pfizer, and Daiichi-Sankyo.

**References**

1. Staerk L, Sherer JA, Ko D, Benjamin EJ, Helm RH. Atrial Fibrillation: Epidemiology, Pathophysiology, and Clinical Outcomes. Circ Res [Internet]. 2017;120(9):1501–17. Available from: https://www.ahajournals.org/doi/pdf/10.1161/CIRCRESAHA.117.309732

2. Jaakkola J, Teppo K, Biancari F, Halminen O, Putaala J, Mustonen P, et al. The effect of mental health conditions on the use of oral anticoagulation therapy in patients with atrial fibrillation: The FinACAF Study. Eur Hear J - Qual Care Clin Outcomes [Internet]. 2021 Oct 22; Available from: https://academic.oup.com/ehjqcco/advance-article/doi/10.1093/ehjqcco/qcab077/6408462

3. Solmi M, Fiedorowicz J, Poddighe L, Delogu M, Miola A, Høye A, et al. Disparities in Screening and Treatment of Cardiovascular Diseases in Patients With Mental Disorders Across the World: Systematic Review and Meta-Analysis of 47 Observational Studies. Am J Psychiatry [Internet]. 2021 Sep 1;178(9):793–803. Available from: http://ajp.psychiatryonline.org/doi/10.1176/appi.ajp.2021.21010031

4. Thrall G, Lip GYH, Carroll D, Lane D. Depression, Anxiety, and Quality of Life in Patients With Atrial Fibrillation. Chest [Internet]. 2007 Oct;132(4):1259–64. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0012369215367222

5. Schmitt SK, Turakhia MP, Phibbs CS, Moos RH, Berlowitz D, Heidenreich P, et al. Anticoagulation in atrial fibrillation: impact of mental illness. Am J Manag Care [Internet]. 2015 Nov 1;21(11):e609-17. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26735294

6. Lunde ED, Joensen AM, Fonager K, Lundbye-Christensen S, Johnsen SP, Larsen ML, et al. Socioeconomic inequality in oral anticoagulation therapy initiation in patients with atrial fibrillation with high risk of stroke: a register-based observational study. BMJ Open [Internet]. 2021 May;11(5):e048839. Available from: https://bmjopen.bmj.com/lookup/doi/10.1136/bmjopen-2021-048839

7. Thomson RM, Niedzwiedz CL, Katikireddi SV. Trends in gender and socioeconomic inequalities in mental health following the Great Recession and subsequent austerity policies: a repeat cross-sectional analysis of the Health Surveys for England. BMJ Open [Internet]. 2018 Aug 30;8(8):e022924. Available from: https://bmjopen.bmj.com/lookup/doi/10.1136/bmjopen-2018-022924

8. Nagasu M, Kogi K, Yamamoto I. Association of socioeconomic and lifestyle-related risk factors with mental health conditions: a cross-sectional study. BMC Public Health [Internet]. 2019 Dec 30;19(1):1759. Available from: https://bmcpublichealth.biomedcentral.com/articles/10.1186/s12889-019-8022-4

9. Fenger-Grøn M, Vestergaard CH, Frost L, Davydow DS, Parner ET, Christensen B, et al. Depression and Uptake of Oral Anticoagulation Therapy in Patients With Atrial Fibrillation. Med Care [Internet]. 2020 Mar;58(3):216–24. Available from: https://journals.lww.com/10.1097/MLR.0000000000001268

10. Fenger-Grøn M, Vestergaard CH, Ribe AR, Johnsen SP, Frost L, Sandbæk A, et al. Association Between Bipolar Disorder or Schizophrenia and Oral Anticoagulation Use in Danish Adults With Incident or Prevalent Atrial Fibrillation. JAMA Netw Open [Internet]. 2021 May 17;4(5):e2110096. Available from: https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2779927

11. Shafrin J, Bognar K, Everson K, Brauer M, Lakdawalla DN, Forma FM. Does knowledge of patient non-compliance change prescribing behavior in the real world? A claims-based analysis of patients with serious mental illness. Clin Outcomes Res [Internet]. 2018 Oct;Volume 10:573–85. Available from: https://www.dovepress.com/does-knowledge-of-patient-non-compliance-change-prescribing-behavior-i-peer-reviewed-article-CEOR

12. Søgaard M, Skjøth F, Kjældgaard JN, Larsen TB, Hjortshøj SP, Riahi S. Atrial fibrillation in patients with severe mental disorders and the risk of stroke, fatal thromboembolic events and bleeding: a nationwide cohort study. BMJ Open [Internet]. 2017 Dec 6;7(12):e018209. Available from: https://bmjopen.bmj.com/lookup/doi/10.1136/bmjopen-2017-018209

13. Teppo K, Jaakkola J, Lehto M, Biancari F, Airaksinen KEJ. The impact of mental health conditions on oral anticoagulation therapy and outcomes in patients with atrial fibrillation: A systematic review and meta-analysis. Am J Prev Cardiol [Internet]. 2021 Sep;7:100221. Available from: https://linkinghub.elsevier.com/retrieve/pii/S2666667721000763

14. Pan A, Sun Q, Okereke OI, Rexrode KM, Hu FB. Depression and Risk of Stroke Morbidity and Mortality. JAMA [Internet]. 2011 Sep 21;306(11):1241. Available from: http://jama.jamanetwork.com/article.aspx?doi=10.1001/jama.2011.1282

15. Michal M, Prochaska JH, Keller K, Göbel S, Coldewey M, Ullmann A, et al. Symptoms of depression and anxiety predict mortality in patients undergoing oral anticoagulation: Results from the thrombEVAL study program. Int J Cardiol [Internet]. 2015 May;187:614–9. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0167527315006324

16. Schnabel RB, Hasenfuß G, Buchmann S, Kahl KG, Aeschbacher S, Osswald S, et al. Heart and brain interactions : Pathophysiology and management of cardio-psycho-neurological disorders. Herz [Internet]. 2021 Mar 5;46(2):138–49. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC7966144

17. Chen LY, Agarwal SK, Norby FL, Gottesman RF, Loehr LR, Soliman EZ, et al. Persistent but not Paroxysmal Atrial Fibrillation Is Independently Associated With Lower Cognitive Function. J Am Coll Cardiol [Internet]. 2016 Mar;67(11):1379–80. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0735109716001583

18. de Bruijn RFAG, Heeringa J, Wolters FJ, Franco OH, Stricker BHC, Hofman A, et al. Association Between Atrial Fibrillation and Dementia in the General Population. JAMA Neurol [Internet]. 2015 Nov 1;72(11):1288. Available from: http://archneur.jamanetwork.com/article.aspx?doi=10.1001/jamaneurol.2015.2161

19. Romiti GF, Pastori D, Rivera-Caravaca JM, Ding WY, Gue YX, Menichelli D, et al. Adherence to the “Atrial Fibrillation Better Care” Pathway in Patients with Atrial Fibrillation: Impact on Clinical Outcomes-A Systematic Review and Meta-Analysis of 285,000 Patients. Thromb Haemost [Internet]. 2021 May 21; Available from: http://www.ncbi.nlm.nih.gov/pubmed/34020488