American Journal of Preventive Cardiology 7 (2021) 100221

Contents lists available at ScienceDirect

American Journal of Preventive Cardiology

journal homepage: www.journals.elsevier.com/the-american-journal-of-preventive-cardiology

The impact of mental health conditions on oral anticoagulation therapy and outcomes in patients with atrial fibrillation: A systematic review and meta-analysis

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ARTICLE INFO

Keywords:
Atrial fibrillation
Oral anticoagulation
Mental health
Psychiatry

ABSTRACT

One third of patients with atrial fibrillation (AF) are estimated to suffer from mental health conditions (MHCs). We conducted a systematic review and meta-analysis to investigate the impact of MHCs on the prevalence and quality of oral anticoagulation (OAC) therapy and outcomes in patients with AF. Medline database was searched for studies published before March 1st 2021 evaluating AF patients with comorbid MHCs reporting on the prevalence of OAC therapy, time in therapeutic range (TTR) in warfarin-receiving patients, adherence to OAC therapy or adverse outcomes (ischemic stroke, hemorrhage or mortality). Studies reporting on outcome events were included in the meta-analysis. The literature search yielded 17 studies including 977,535 patients that fulfilled the inclusion criteria of this review. AF patients with MHCs had a lower prevalence of OAC use and poorer TTR compared with patients without MHCs. Evidence on OAC quality in patients receiving direct oral anticoagulants (DOACs) was minimal and inconclusive. A decrease in depression-associated deficit in OAC prevalence was observed after the introduction of DOACs. Pooled analysis of five studies reporting on outcomes showed that MHCs were an independent risk factor for both stroke (RR 1.25, 95%CI 1.08–1.45, I^2 0%) and major bleeding (RR 1.17, 95%CI 1.08–1.27, I^2 27%). Data on mortality were lacking and therefore not included in the meta-analysis. Evidence on the impact of specific MHCs on the outcomes were inadequate. In conclusion, MHCs are independent risk factors for stroke and major bleeding in patients with AF. Future studies are needed to confirm the findings of this meta-analysis, to evaluate the prognostic impact of different MHCs and to clarify whether the introduction of DOACs might have improved the outcomes of these patients.

1. Introduction

Atrial fibrillation (AF) is a common arrhythmia affecting approximately 3% of the adult population in developed countries [1]. It is an important risk factor of ischemic stroke observed in up to 38% of all stroke patients and is also associated with increased mortality [1–4]. Oral anticoagulation (OAC) treatment is effective in reducing the risk of stroke in AF patients, although as a drawback, bleeding risk is somewhat increased [5]. Mental health conditions (MHC) have a lifetime prevalence of up to 46% in the developed countries and are associated with high prevalence of cardiovascular risk factors and increased cardiovascular morbidity and mortality [6–9]. Previous studies indicate that the prevalence of MHCs in AF patients may be over 30% [10–13]. Patients affected by severe MHCs have a life expectancy reduced by as much as 15–20 years compared with the general population, mainly due to somatic morbidities which are often undertreated [14–21]. Cardiovascular diseases are the single most important contributor to the elevated mortality rate observed in MHC patients [18]. Additionally, there is evidence of MHCs per se increasing the risk of stroke, regardless of the presence of AF[22,23]. However, the impact of MHCs on outcomes in AF patients remains unclear[12,22–25]. We conducted a systematic review to provide a comprehensive overview of the current evidence regarding the impact of MHCs on the quality of OAC therapy and a meta-analysis to pool the adjusted impact of MHCs on adverse outcomes in AF patients.

2. Methods

The present systematic review and meta-analysis (PROSPERO reference CRD42021248368) were performed in accordance with the Pre-

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https://doi.org/10.1016/j.ajpc.2021.100221
Received 30 April 2021; Received in revised form 2 June 2021; Accepted 24 June 2021

ferred Reporting Items for Systematic Reviews and MetaAnalysis guidelines [26].

2.1. Literature search

A systematic review of the literature investigating the effects of MHCs on the prevalence and quality of OAC therapy as well as outcomes in patients with AF was performed on March 1, 2021 through PubMed. The following Medical Subject Heading (MESH) terms were used to search for eligible articles: (”atrial fibrillation” OR ”atrial flutter”) AND (”mental health condition” OR ”psychiatric disorder” OR ”depression” OR ”bipolar disease” OR ”anxiety” OR ”psychotic disorder” OR ”schizophrenia” OR ”post-traumatic stress disorder”) AND (”oral anticoagulation therapy” OR ”warfarin” OR ”novel oral anticoagulant” OR ”vitamin K antagonist”) AND (”bleeding” OR ”ischemic stroke” OR ”hemorrhage” OR ”outcomes” OR ”time in therapeutic range” OR ”adherence” OR ”prescription rate” OR ”mortality”).

The inclusion criteria for this study were: 1) study population affected by any MHC, 2) study reporting on the prevalence of OAC therapy in AF patients, time in therapeutic range (TTR) in patients receiving warfarin, adherence to OAC therapy or outcome of interest, i.e. mortality, ischemic stroke and/or bleeding event; 3) study published in English. The literature search was performed without study design, publication year or geographical restrictions. The selection of articles was carried out in three steps. First, publication titles were reviewed and articles not matching the inclusion criteria were excluded. Second, the remaining articles underwent full-text review, and the articles reporting on the effects of MHCs on either OAC use, anticoagulation control or outcomes in AF patients were included in the review. The articles reporting on the multivariable adjusted impact of any MHC on risk of ischemic stroke or any major bleeding were included in the meta-analysis. Third, references of included articles were screened to identify studies not detected by the initial search strategy.

2.2. Statistical analysis

Statistical analyses were conducted using Stata v. 15.1 (StataCorp LLC, Texas, USA) statistical software. The natural logarithm of adjusted hazard ratios for different outcomes along with their 95% confidence intervals were estimated and pooled using random-effects analysis. Heterogeneity across the studies was evaluated using the I^2 test. I^2 less than 40% was considered not significant. Analyses were performed using the metan command. P-values <0.05 were considered statistically significant.

3. Results

The literature search yielded 17 studies including 977,535 patients fulfilling the inclusion criteria of this analysis (Fig. 1).

3.1. Prevalence of oral anticoagulation use in AF patients with MHCs

Eight studies reported on the prevalence of OAC therapy among AF patients with MHCs. Most of them documented a lower rate of OAC use among patients suffering from MHCs (Table 1). Two studies reported on a lower rate of warfarin prescriptions in OAC-eligible AF patients suffering from any MHC compared with those without MHCs[27,28]. Concerning specific MHCs, depression was recently detected to predict lower initiation and prevalence of OAC therapy among AF patients in two large Danish nationwide cohort studies, whilst Schmitt et al. did not observe any association between depression and warfarin prescription rate[25,28,29]. Among four small studies dealing with geriatric patients, only one study documented an association between depressive symptoms and absence of OAC therapy [30–33]. Schizophrenia, bipolar disease, anxiety disorders and psychotic disorders were also associated

Table 1
Characteristics of studies reporting MHCs impact on prevalence of OAC therapy for atrial fibrillation.

Study	Country	Study design	No. of patients	Study interval	MHC	Effect on OAC prevalence
De Breucher et al. [33]	Belgium	Retrospective observational study	768	2006–2008	Depression	No effect[e]
Denoël et al. [32]	Belgium	Observational study	142	2011–2012	GDS>1	0.72 (0.35–1.46)[d]
Fenger-Grøn et al. [29]	Denmark	Nationwide retrospective cohort study	192,656[b]	2005–2016	Depression	–4.2% (–4.7 - –3.8)[c]
Saczynski et al. [31]	USA	Cross-sectional study	1244	2016–2018	Depression	0.79(0.49–1.27)[a]
Sánchez-Barba et al. [30]	Mexico	Cross-sectional study	137	2008–2013	GDS>5	0.19 (0.07–0.54)[a]
Schmitt et al. [28]	USA	Retrospective cohort study	125,670	2004	Any MHC	0.90 (0.87–0.94)[a]
					Anxiety Disorders	0.86 (0.80–0.93)[a]
					Psychotic disorders	0.77 (0.65–0.90)[a]
					Depression	0.96 (0.91–1.02)[a]
					PTSD	0.99 (0.84–1.17)[a]
					Other MHC	1.05 (0.92–1.19)[a]
Søgaard et al. [25]	Denmark	Nationwide retrospective cohort study	253,741	2000–2015	Severe depression, bipolar disorder and schizophrenia	Lower rate of OAC therapy initiation[e]
Walker et al. [27]	USA	Retrospective chart review	296	2003	Any MHC	0.42 (0.22–0.77)[a]

Abbreviations: GDS, Geriatric Depression Scale; MHC, mental health condition; OAC, oral anticoagulation; PTSD, post-traumatic stress disorder.

[a] Adjusted odds ratio.
[b] Prevalent AF patients.
[c] Adjusted proportion difference.
[d] Odds ratio.
[e] Risk estimate not reported.

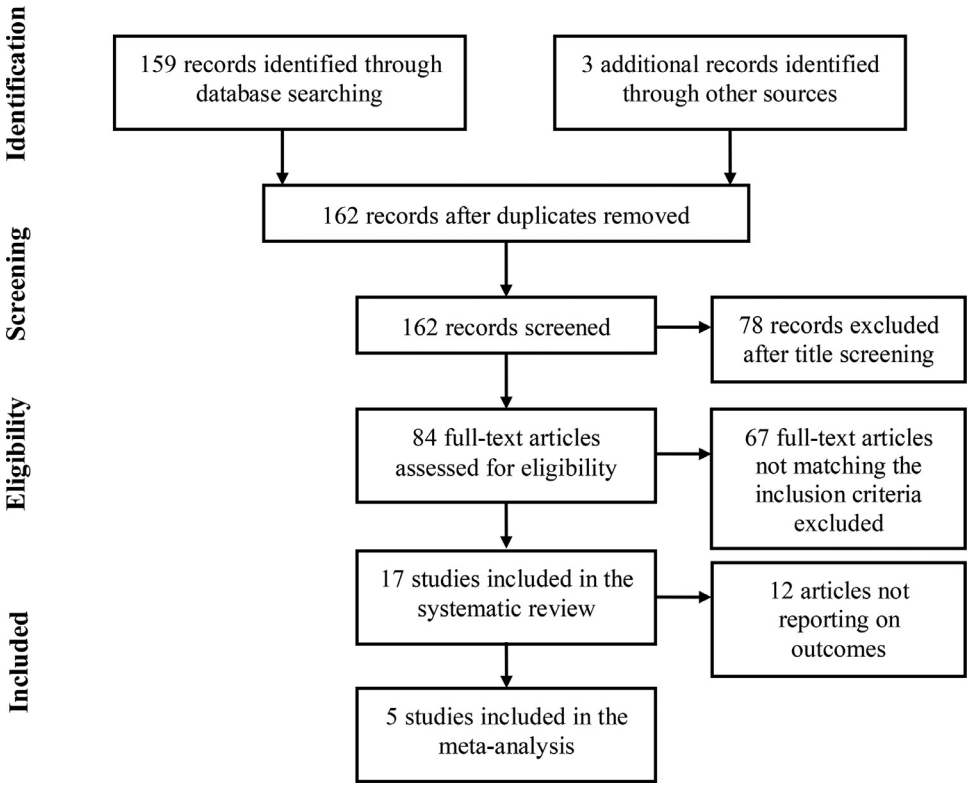

Fig. 1. Study flowchart.

with lesser use of OACs in AF patients in isolated reports[25,28]. Importantly, a substantial increase in overall OAC use and a decrease in depression-associated underuse of OAC therapy was noted after the introduction of direct oral anticoagulants (DOAC) [29].

3.2. Quality of anticoagulation in patients with MHCs

Eight studies assessed the quality of anticoagulation, as measured by TTR or OAC adherence, among patients with MHCs. Four studies focused on OAC use in AF patients, and four studies included also patients with other indications for OAC therapy[12,24,27,34–38]. The characteristics of these studies are described in Table 2.

In general, psychiatric disorders had a stronger negative effect than somatic comorbidities on TTR [34]. Bipolar disorder and depression were associated with time out of target international normalized ratio (INR) range in three studies[12,34,35]. Lower TTR was observed in patients with depression and in those with combined depression and anxiety compared with patients without these conditions by Baumgartner et al [24]. Supratherapeutic INR values were more common in patients with any MHC and correlated with a depressive Geriatric Depression Scale score[27,36]. In the only study among patients receiving DOAC treatment depression was associated with poor self-reported adherence to medication [37]. On the other hand, a small questionnaire survey demonstrated no association between self-reported depression and OAC adherence in AF patients [38].

Other MHCs including anxiety disorder, post-traumatic stress disorder and schizophrenia, have not been associated with poor TTR, except for the sole finding of lower TTR in patients with psychotic disorders other than schizophrenia [12]. Paradise et al. showed that higher psychiatric symptom severity and a history of psychiatric hospitalization predicted lower TTR [12].

3.3. Adverse outcomes in AF patients with MHCs

Adverse outcomes among AF patients with MHCs were investigated in five studies and their characteristics are summarized in Table 3. Patient characteristics of these studies are presented in Table 4 in the supplementary material. The pooled results of the effect of any MHC on the risk of ischemic stroke or any major bleeding are presented in Fig. 2.

Three studies reported on the association between MHCs and the risk of ischemic stroke in AF patients. Pooled analysis of adjusted risk estimates showed that MHC of any nature was associated with a higher risk of ischemic stroke in patients with AF (pooled adjusted HR 1.25, 95% CI: 1.08–1.45, $I^2 = 0\%$), without significant heterogeneity between studies. Pooled analysis of the prognostic impact of specific MHCs was not feasible because only one study showed an association between anxiety and a composite outcome of ischemic stroke and intracranial hemorrhage [24]. (Table 3).

Major bleeding events in AF patients with MHCs were reported in five studies. All reported bleeding events were major, and risk estimates of intracranial, traumatic intracranial, extracranial, gastrointestinal, or any major hemorrhage were pooled in the meta-analysis as risk of any major bleeding event. Pooled adjusted risk estimates showed that MHC of any nature was independently associated with a significantly higher risk of major bleeding in patients with AF (HR 1.17, 95% CI: 1.08–1.27, $I^2 = 26.5\%$), with low heterogeneity between studies. Regarding specific MHCs, an association between psychotic disorders other than schizophrenia and risk of major hemorrhage was observed in one study, and as described above, higher adjusted odds of a composite outcome of ischemic stroke and intracranial hemorrhage in AF patients suffering from anxiety disorders was reported in another study[12,24]. Increased risk of traumatic intracranial bleeding was reported among depressed patients aged over 75 years receiving warfarin for AF [39]. Otherwise, there is currently no evidence of increased bleeding risks associated with different types of MHCs (Table 3). Additionally, neither psychiatric symptom severity nor psychiatric hospitalization history were shown to impact the risk of bleeding [12].

No study reported on all-cause or cardiovascular mortality among AF patients with MHCs, although an increased risk of fatal thromboembolism was observed in patients with schizophrenia, but not in those with severe depression or bipolar disease in a single study [25].

Table 2
Characteristics of studies reporting on the impact of MHCs on the quality of OAC therapy.

Study	Country	Study design	No. of patients	Study interval	Investigated effect	
Baumgartner et al. [24]	USA	Retrospective Cohort Study	25,570	2004–2007	MHC on TTR%[d]	
					No anxiety or depression	57%
					Anxiety	57%
					Depression	52%**
					Anxiety and depression	53%**
Diug et al. [36]	Australia	Case–control study	157 cases 329 controls	2008–2009	GDS ≥2 on INR ≥6.0	2.1 (1.3–3.5)[c,*]
Emren et al. [37]	Turkey	Cross-sectional study	2738	2015–2016	Depression on poor DOAC adherence	1.94 (1.47–2.57)[c,**]
Paradise et al. [12]	USA	Retrospective cohort study	103,897	2007–2008	MHC on TTR%[a]	
					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. [35]	USA	Retrospective cohort study	103,897	2006–2008	MHC on percent time below and above INR target[a]	
					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. [34]	USA	Retrospective cohort study	124,619	2006–2008	MHC on TTR%[a]	
					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. [38]	Japan	Questionnaire survey	378	2014	Self-reported depression on adherence	0.74 (0.26–2.64)[b]
Walker et al. [27]	USA	Retrospective chart review	296	2011–2012	Any MHC on INR>5	15.9 (1.6–154.1)[e]

Abbreviations: DOAC, direct oral anticoagulant; GDS Geriatric depression scale; INR, international normalized ratio; MHC, mental health condition; PTSD, post-traumatic stress disorder; TTR, time in therapeutic range;.

[a] Adjusted effect (95% confidence interval).
[b] Hazard ratio (95% confidence interval).
[c] Odds ratio (95% confidence interval).
[d] Absolute TTR value.
[e] Adjusted odds ratio (95% confidence interval).
* $p < 0.05$.
** $p < 0.001$.

4. Discussion

The present systematic review and meta-analysis showed that the presence of any MHC is independently associated with an increased risk for both ischemic stroke and major bleeding in patients with AF. Lack of data prevented more in-depth analyses on the impact of MHCs on mortality as well as on the effect of specific MHCs on adverse outcomes. Overall, the available data suggest that OAC therapy is less frequently prescribed in AF patients suffering from MHCs. Anticoagulation quality as measured by TTR was also worse among patients with MHCs receiving warfarin. Importantly, data from the DOAC era were scarce and only one study of small size reported on depression as a predictor of poor therapy adherence.

Our meta-analysis demonstrated that AF patients with any MHC have approximately 25% higher adjusted ischemic stroke risk and 17% higher bleeding risk compared to patients without MHCs. These findings are concordant with two previous meta-analyses that have shown depression and anxiety to be independent risk factors of stroke, regardless of the presence of AF[22,23]. Additionally, ischemic stroke and bleeding risks among AF patients with MHCs are likely further increased due to higher prevalence of ischemic stroke and bleeding risk factors, lower prevalence of OAC use and poorer quality of OAC therapy as measured by TTR and medication adherence[24,25,28] (Tables 1 and 2). Improvement of OAC coverage and quality are key factors to reduce the risk of ischemic stroke and bleeding events also in this patient group.

In addition to the high prevalence of classical cardiovascular risk factors and lower prevalence and quality of OAC therapy, there are likely further mechanisms underlying the observed higher ischemic stroke and bleeding risks among patients with MHCs. Higher levels of systemic inflammation have been observed in patients with MHC, and systemic

Table 3
Characteristics of studies reporting on the impact of MHCs on the outcome of patients with atrial fibrillation.

Study	Country	Study design	No. of patients	Study interval	MHC	Outcome	Adjusted hazard ratio
Dodson et al. [39]	USA	Retrospective cohort study	31,951	2001–2012	Depression	Traumatic ICH	1.30(1.05–1.61)*
Baumgartner et al. [24]	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. [12]	USA	Retrospective cohort study	103,897	2007–2008	Any MHC	Major hemorrhage	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. [61]	USA	Retrospective cohort study	9345	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. [25]	Denmark	Nationwide retrospective cohort study	253,741	2000–2015	Schizophrenia	Ischemic stroke	1.37 (0.88–2.14)
						Fatal TE	3.16 (1.78–5.61) *
						Major bleeding	1.37 (0.99–1.90)
					Severe depression	Ischemic stroke	1.36 (0.89–2.08)
						Fatal TE	1.31 (0.67–2.56)
						Major bleeding	1.25 (0.87–1.78)
					Bipolar disease	Ischemic Stroke	1.04 (0.69–1.56)
						Fatal TE	1.53 (0.93–2.53)
						Major bleeding	0.82 (0.58–1.15)

Abbreviations: ECH, extracranial hemorrhage; GI, gastrointestinal; ICH, intracranial hemorrhage; MHC, mental health condition; GAF, global assessment of functioning. PTSD, post-traumatic stress disorder; TE, thromboembolism.
* $p < 0.05$.

inflammation has been associated with increased ischemic stroke and bleeding risks in AF patients [40–42]. Autonomic nervous dysfunction in psychiatric disorders has been suggested as one underlying mechanism in the increased cardiovascular disease burden but has not been studied in the context of MHC and AF outcomes [43–45]. Lifestyle related risk factors, including obesity, excessive alcohol use and smoking are common among patients with MHCs and are likely to contribute to higher stroke and bleeding risks in this patient group [46–50]. Additionally, many psychotropic medications have adverse metabolic effects increasing the cardiovascular risk burden and have also been independently associated with increased bleeding and stroke risks [51–54].

The available studies documented a lower prevalence of OAC use in AF patients with MHCs compared to those without these conditions. Large heterogeneity was, however, noted regarding specific conditions. There are several potential factors contributing to the observed OAC deficit. First, patients with MHCs have more often contraindications for OAC therapy [28]. Physicians may also occasionally choose to withhold OAC therapy owing to additional concerns of elevated bleeding risks in these patients due to the antithrombotic effects of antidepressants, excessive alcohol consumption, increased risk of falling or concern of poor medication adherence[12,37,39,55,56]. These trepidations regarding safety of OAC treatment are often justified, but they may also at times be unfounded and based on physician bias and prejudice [57]. Fragmented care due to the separation of psychiatric and somatic healthcare services may also cause treatment barriers.

TTR was in general lower among warfarin-receiving patients with MHCs than in those without. Excessive alcohol use and substance abuse are common among patients with MHCs and have been associated with low TTR values and supratherapeutic INR values[25,34,46,58]. Poor OAC control in this group is likely related to alcohol enhancing the antithrombotic effects of warfarin as well as deficits in patients' self-care capabilities, which are likely to impair systematic INR follow-up [56] Nonadherence to medication is common in patients with MHCs and may also affect poor OAC conrol [59,60]. Emren et al. reported depression as a predictor of poor adherence to OAC treatment, although two other studies observed no such connection[29,37,38]. Currently, there are no reports on the effects of other MHCs on OAC adherence.

Although the reviewed studies demonstrated consistently inferior OAC prevalence and quality in AF patients with MHCs in the past decades, interestingly an increase in overall OAC uptake and a decrease in depression-associated OAC deficit was noted during the follow-up period by Fenger-Grøn et al [29]. This may be related to the emergence of the easier-to-use DOACs which reduce safety concerns and demands for patients' self-care capabilities. Additionally, through new research and guidelines on AF, the general awareness of the condition, its treatment and potential complications has considerably increased over the past decade, probably also having a positive effect on the quality of OAC

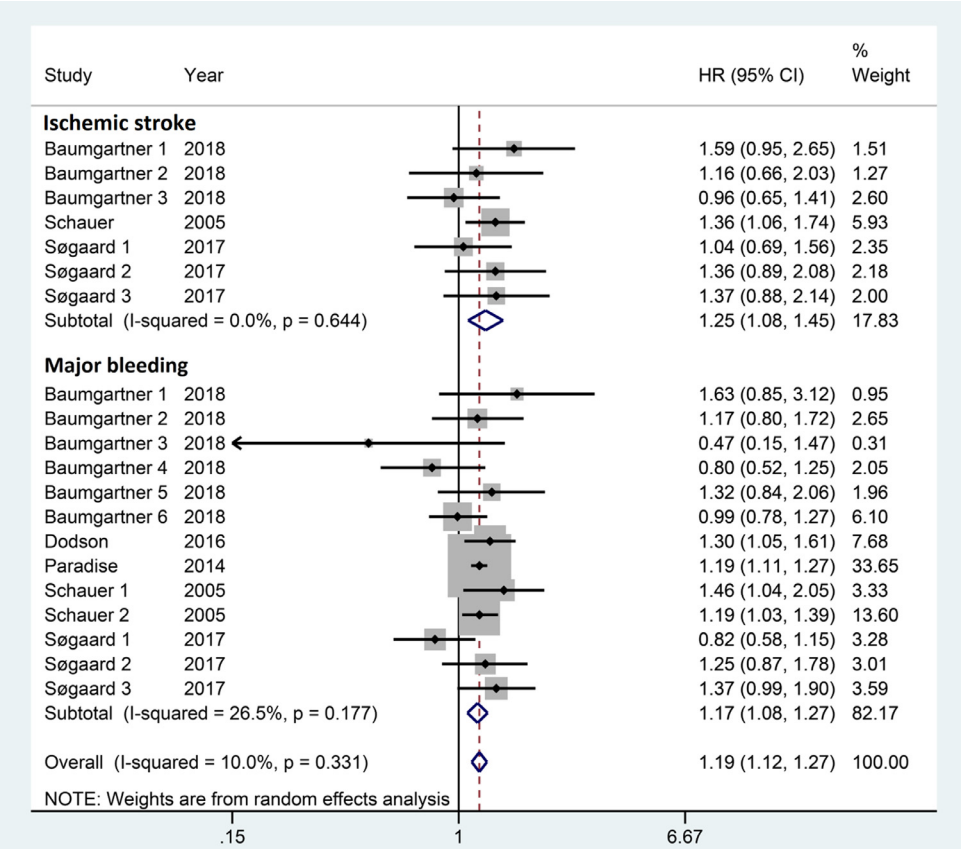

Fig. 2. Forest plot of pooled risk estimates of ischemic stroke and any major bleeding in atrial fibrillation patients with MHC compared with patients without MHC. Risk estimates >1 indicate higher risk of adverse events for patients with MHCs.

therapy in patients with MHCs as well. To further improve the treatment of AF patients with MHCs, the previously described factors behind poor prevalence and quality of OAC therapy must be tackled. This includes improving patient education and physicians' awareness of the safe use of OAT in these patients and as well as lowering their barriers in health care access and improving the collaboration between somatic and mental health services.

The results of our meta-analysis must be interpreted within the context of several limitations. The meta-analysis included a limited number of studies, which utilized varying definitions of MHCs and outcome variables. Although low heterogeneity was noted in the effects of the studies in the meta-analysis, some degree of publication bias cannot be excluded. Outcome data ranging up to the DOAC era were limited. Most of the reviewed outcome studies included only patients already receiving warfarin therapy and thus considered suitable recipients of OAC treatment. Although Søgaard et al. also included AF patients without OAC therapy, they were limited by the exclusion of patients treated outside the hospital arrangement. A notable limitation is that there was heterogeneity regarding the confounding variables used in the adjustment of risk estimates across the studies included in the meta-analysis. Therefore, the possibility of residual confounding not addressed by these adjustments cannot be excluded. Data on alcohol consumption, smoking, exercise, and other lifestyle related risk factors were incompletely monitored in the outcome studies, possibly biasing the results. We included only studies published in English, which may also contribute some bias. Finally, mortality data were lacking.

The reasons underlying low OAC prescription rate and poor OAC quality among patients with MHC deserve more attention. Data on the prevalence and quality of OAC therapy are derived mainly from studies with small sample sizes conducted during the early 2000s and dealing mainly with warfarin therapy. Indeed, more information is needed on whether the MHC-associated deficit in OAC treatment of AF has persisted in the era of the easier-to-use DOACs. Moreover, it would be of clinical interest to investigate how the introduction of DOACs has impacted the bleeding, ischemic stroke, and mortality outcomes of AF patients with MHCs. The effects of specific MHCs on adverse outcomes in AF patients need to be determined, and the mechanisms underlying the increased risk of ischemic stroke and bleeding outcomes in patients with MHCs need to be investigated further. Importantly, mortality data of AF patients with MHCs is required to achieve a comprehensive view on the overall risk-to-benefit ratio of OAC therapy in different patient groups. More solid evidence on these aspects may be expected from the nationwide FinACAF study, which includes all Finnish patients recorded with a diagnosis of AF during 2004–2018 at any level of care (Clinicaltrials.gov identifier: NCT04645537).

5. Conclusions

This systematic review and meta-analysis demonstrated that MHCs are associated with lower prevalence and quality of OAC therapy as well as higher risk of ischemic stroke and major bleeding events in patients with AF. Future studies are required to confirm these findings, to assess the impact of specific MHCs on adverse outcomes and to evaluate whether DOACs might increase therapy adherence and safety over warfarin in this patient population.

Author contributions

Konsta Teppo: Conceptualization, Data curation, Investigation, Writing - original draft; Jussi Jaakkola: Conceptualization, Investigation, Project administration, Writing - review & editing; Mika Lehto: Conceptualization, Project administration, Supervision, Writing - review & editing; Fausto Biancari: Conceptualization, Formal Analysis, Methodology, Supervision, Writing - review & editing; Juhani Airaksinen: Conceptualization, Project administration, Supervision, Writing - review & editing.

Funding

None.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

None to declare.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ajpc.2021.100221.

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