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The Effects of Warfarin and Novel Oral Anticoagulants on Depression and Anxiety in Patients with Non-Valvular Atrial Fibrillation

Non-Valvüler Atriyal Fibrilasyon Hastalarında Warfarin ve Yeni Nesil Oral Antikoagülan İlaçların Depresyon ve Anksiyete Üzerindeki Etkileri

ABSTRACT

Objective: Atrial fibrillation (AF) is the most prevalent cardiac arrhythmia and has a detrimental impact on psychological well-being. This study aims to determine the prevalence of anxiety and depression in patients with non-valvular AF and to investigate the relationship between these psychological conditions and the treatment regimens administered.

Method: This cross-sectional study included 255 individuals diagnosed with non-valvular AF who were treated between 2021 and 2022. Psychiatric evaluation was conducted using the Beck Depression Inventory and Beck Anxiety Inventory. Multivariate regression analysis was performed to identify predictors of depression and anxiety.

Results: Of the patients included, 62 were on warfarin, 124 were on novel oral anticoagulants (NOACs), and 69 were not receiving any oral anticoagulant (OAC) therapy. Overall, 68.6% had depression and 64.7% had anxiety at a moderate or higher severity level. Although there was no notable variation in anxiety and depression scores between patients on NOACs and those not undergoing OAC treatment, the warfarin group had significantly higher scores than the other two groups. Age, anxiety, C-reactive protein (CRP) levels, and CHA2DS2-VASc scores (Congestive heart failure, Hypertension, Age ≥ 75 years, Diabetes mellitus, prior Stroke/transient ischemic attack-Vascular disease, Age 65-74 years, Sex category) all positively correlated with the severity of depression. Anxiety, in turn, was positively associated with age, depression, and CHA2DS2-VASc scores, and negatively associated with ejection fraction. Regression analysis revealed a strong correlation between warfarin treatment and anxiety severity.

Conclusion: The findings of this study suggest that warfarin treatment is associated with significant psychological effects in patients with AF. Considering that comorbid psychiatric disorders are linked to unfavorable prognosis and higher mortality, the development of appropriate intervention strategies that address psychological distress as part of the treatment process may provide substantial clinical benefits.

Keywords: Anxiety, atrial fibrillation, depression, novel oral anticoagulants, warfarin

ÖZET

Amaç: Atriyal fibrilasyon (AF), kardiyak aritmilerin en sık nedeni olup psikolojik iyi oluş üzerinde olumsuz etkilere sahiptir. Bu çalışmanın amacı, non-valvüler AF hastalarında depresyon ve anksiyete prevalansını değerlendirmek ve bu psikolojik durumlar ile uygulanan tedavi rejimleri arasındaki ilişkiyi incelemektir.

Yöntem: Kesitsel nitelikteki bu çalışma, 2021-2022 yılları arasında non-valvüler AF tanısı ile tedavi gören toplam 255 hastayı kapsamaktadır. Hastaların psikolojik değerlendirmelerinde Beck Depresyon ve Beck Anksiyete Envanteri kullanılmıştır. Depresyon ve anksiyetenin belirleyicilerini tespit etmek amacıyla çok değişkenli regresyon analizi uygulanmıştır.

Bulgular: Çalışmaya dahil edilen hastaların 62'si warfarin, 124'ü yeni nesil oral antikoagülan (NOAK) kullanırken, 69'u herhangi bir oral antikoagülan (OAK) tedavisi almamaktaydı. Orta ve üstü şiddet baz alındığında, hastaların %68.6'sında depresyon, %64.7'sinde anksiyete tespit edilmiştir. NOAK kullanan hastalar ile herhangi bir OAK tedavisi almayan hastalar arasında anksiyete ve depresyon puanları açısından anlamlı bir fark bulunmazken, warfarin kullanan grupta diğer iki gruba kıyasla anlamlı derecede daha yüksek bulunmuştur. Depresyon şiddeti, yaş, anksiyete, CRP ve CHA2DS2-VASc puanları ile pozitif korelasyon göstermiştir. Anksiyete ise yaş, depresyon ve CHA2DS2-VASc skoru ile pozitif, ejeksiyon fraksiyonu ile negatif korelasyona sahipti. Regresyon analizi, warfarin tedavisinin anksiyete şiddetini öngörmede önemli faktörlerden biri olduğunu göstermiştir.

ORIGINAL ARTICLE
KLİNİK ÇALIŞMA

Neslihan Cansel[1]
Muhammed Yasin Adıgüzel[2]
Şahide Nur İpek Melez[3]
Adil Bayramoğlu[4]

[1]*Department of Psychiatry, İnönü University Faculty of Medicine, Malatya, Türkiye*
[2]*Department of Cardiology, Malatya Training and Research Hospital, Malatya, Türkiye*
[3]*Department of Internal Medicine, Gaziantep City Hospital, Gaziantep, Türkiye*
[4]*Department of Cardiology, İnönü University Faculty of Medicine, Malatya, Türkiye*

Corresponding author:
Adil Bayramoğlu
✉ adilbayramoglu@gmail.com

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Sonuç: Çalışmamızın bulguları, warfarin kullanımının AF hastalarında belirgin psikolojik etkilere neden olduğunu ortaya koymaktadır. Eşlik eden psikiyatrik hastalıkların kötü prognoz ve artmış mortalite ile ilişkili olduğu göz önünde bulundurulduğunda, hastaların tedavi sürecinde ruhsal sıkıntılarının da ele alındığı uygun müdahale stratejilerinin geliştirilmesi önemli klinik faydalar sağlayabilir.

Anahtar Kelimeler: Anksiyete, atriyal fibrilasyon, depresyon, yeni nesil oral antikoagülanlar, warfarin

Atrial fibrillation (AF) is the most common cardiac arrhythmia, with its prevalence increasing with age and affecting approximately 1–4% of the global population. Although AF can present with a wide range of symptoms, nearly one-third of patients may remain asymptomatic.[1,2] AF is strongly associated with increased morbidity and mortality due to heart failure, stroke, and other thromboembolic events. Compared to healthy individuals, patients with AF have a threefold higher risk of developing heart failure and a fivefold higher risk of stroke.[3,4] The rising medical costs associated with AF also contribute to its substantial socioeconomic burden.[5]

Oral anticoagulant (OAC) therapy plays a crucial role in the management of AF, primarily by reducing the risk of cardioembolic events.[6] Current guidelines recommend OAC therapy not only for patients with AF but also for all individuals with a CHA_2DS_2-VASc score (Congestive heart failure, Hypertension, Age ≥ 75 years, Diabetes mellitus, prior Stroke/transient ischemic attack–Vascular disease, Age 65–74 years, Sex category) of ≥ 2.[7] Although vitamin K antagonists (VKAs), such as warfarin, are effective in preventing stroke, their clinical use is limited by several challenges, including food–drug interactions, a narrow therapeutic window, the need for frequent international normalized ratio (INR) monitoring, bleeding risks, and associated costs. These factors collectively contribute to reduced patient satisfaction and poor medication adherence. In contrast, novel oral anticoagulants (NOACs) have become increasingly preferred in recent years due to their predictable anticoagulant effects, lack of need for routine bleeding monitoring, and minimal drug and food interactions.[8]

Patients with AF experience depression and anxiety more frequently than the general population. Contributing factors may include reduced quality of life, functional impairment, and the direct biological effects of the underlying cardiac condition.[9] Conversely, pre-existing anxiety and depression may contribute to the development of functional somatic disorders through behavioral, pathophysiological, genetic, and iatrogenic mechanisms. These conditions can significantly impair treatment adherence and further diminish quality of life.[10] Furthermore, these mental health disorders may increase the frequency of AF episodes and elevate the risk of complications such as heart failure and mortality.[11,12] Therefore, effective prevention and management of AF requires the identification and addressing of psychosocial risk factors.

Recent studies have shown that OAC therapy can affect the psychological well-being of patients with AF, with warfarin use being particularly associated with increased symptoms of depression and anxiety.[9,13] However, these studies have often been limited by small sample sizes and have primarily focused on comparisons among patients receiving different types of oral anticoagulants, without accounting for the severity of psychiatric symptoms in individuals not receiving any anticoagulant therapy. This study aims to assess the prevalence of depression and anxiety among patients with non-valvular atrial fibrillation (NVAF) and to investigate potential associations between these psychiatric conditions and the type of anticoagulant therapy administered.

ABBREVIATIONS

AF	Atrial fibrillation
ANOVA	Analysis of variance
BAI	Beck Anxiety Inventory
BDI	Beck Depression Inventory
CHF	Congestive heart failure
CRP	C-reactive protein
CRT	Cardiac resynchronization therapy
DM	Diabetes mellitus
HGB	Hemoglobin
INR	International normalized ratio
MI	Myocardial infarction
NOAC	Novel oral anticoagulant
NVAF	Non-valvular atrial fibrillation
PVD	Peripheral vascular disease
TSH	Thyroid-stimulating hormone
VKA	Vitamin K antagonist

Materials and Methods

Patients and Study Protocol

This study was conducted among patients diagnosed with NVAF who attended the cardiology outpatient clinic between 2021 and 2022. Participation was entirely voluntary, and informed consent was obtained from all patients. The following exclusion criteria were applied:

- Current treatment for pulmonary embolism and/or deep vein thrombosis
- Presence of an endocrine disorder other than diabetes mellitus requiring treatment
- Active or chronic psychiatric illness
- Diagnosed dementia
- Cardiac resynchronization therapy (CRT) within the last six months
- Recent transition between warfarin and NOAC therapy within the past three months
- Major surgery or trauma within the last three months
- History of malignancy.

The CHA_2DS_2-VASc score was calculated based on the presence of the following factors, with corresponding points assigned: congestive heart failure (1), hypertension (HT) (1), age ≥ 75 years (2), diabetes mellitus (DM) (1), prior stroke or transient ischemic attack (2), vascular disease (1), age 65–74 years (1), and female sex (1). The maximum possible CHA_2DS_2-VASc score was nine points. Vascular disease was defined as a history of myocardial infarction (MI), peripheral vascular disease (PVD), or aortic plaque formation. Peripheral arterial disease was defined as at least 50% stenosis in non-coronary arteries. Left ventricular systolic dysfunction was classified as an ejection fraction ≤ 40% in patients with congestive heart failure. HT was defined as a systolic and/or diastolic blood pressure ≥ 140/90 mmHg, a previous diagnosis of HT, or the use of antihypertensive medication.[14] DM was defined as a fasting blood glucose level ≥ 126 mg/dL, a two-hour postprandial glucose level ≥ 200 mg/dL, or the use of glucose-lowering medication.[15]

Laboratory parameters, including C-reactive protein (CRP), hemoglobin (HGB), fasting blood glucose, creatinine, and thyroid-stimulating hormone (TSH), were recorded at the time of study enrollment.

Data Collection Tools

Psychiatric assessment of the participants was conducted using the Beck Depression Inventory and the Beck Anxiety Inventory.

Beck Depression Inventory (BDI)

The BDI was used to evaluate the severity of depressive symptoms in the patients. Developed by Beck in 1961,[16] the Turkish adaptation and validation study of this scale was conducted by Hisli et al.[17] The BDI comprises 21 items, each rated on a four-point Likert scale. The maximum attainable score is 63. Results are classified as follows: 0–9, no/minimal depression; 10–18, mild depression; 19–29, moderate depression; and 30–63, severe depression.[18]

Beck Anxiety Inventory (BAI)

The BAI, designed by Beck et al.,[19] assesses anxiety symptoms in individuals. This self-report scale consists of 21 items, each scored from 0 to 3. A total score between 0 and 7 reflects minimal anxiety, scores between 8 and 15 correspond to mild anxiety, scores from 16 to 25 represent moderate anxiety, and scores from 26 to 63 indicate severe anxiety. The Turkish adaptation and validation of the scale were carried out by Ulusoy et al. in 1996.[20]

Ethical approval for the study was obtained from İnonü University Non-Invasive Clinical Research Ethics Committee (Approval Number: 2021/2369, Date: 07.09.2021). The research was conducted in accordance with the principles outlined in the Declaration of Helsinki. Throughout the preparation of this study, no artificial intelligence (AI)-driven tools, including large language models (LLMs), chatbots, or image generation technologies, were employed.

Statistical Analysis

All statistical analyses were performed using SPSS software, version 26.0 (SPSS Inc., Chicago, IL, USA). Based on their history of oral anticoagulant use, patients were divided into three groups: (1) those not receiving anticoagulant therapy (including individuals who declined treatment upon recommendation), (2) those receiving NOACs, and (3) those receiving warfarin.

One-way analysis of variance (ANOVA) was used to compare continuous variables across groups, while the chi-square (χ^2) test was used for categorical variables. Continuous variables are presented as mean ± standard deviation (SD) and/or median (minimum–maximum), whereas categorical variables are summarized as frequencies and percentages.

Pearson correlation analysis was conducted to examine the relationship between depression and anxiety scores and clinical variables. Additionally, multiple logistic regression analysis was performed to identify independent predictors of depression and anxiety.

Results

Characteristics of the Patients

A total of 255 patients participated in the study, consisting of 133 women and 122 men. Among them, 69 patients were not on anticoagulant treatment, 124 were on NOACs, and 62 were on warfarin. Statistically significant age differences were observed across the groups ($P < 0.001$), with Group 1 (no anticoagulant) having a younger mean age (53 ± 18 years) compared to Group 2 (NOACs, 69 ± 11 years) and Group 3 (warfarin, 70 ± 10 years). Age distribution also showed significant variation (< 65, 65–75, > 75) ($P < 0.001$). Group 1 had a greater proportion of patients under 65 years, while Groups 2 and 3 included a larger proportion of patients aged 65–75 and over 75 years.

The incidence of heart failure did not differ significantly across the groups ($P = 0.335$). However, significant differences were observed in the incidence of hypertension, diabetes mellitus, and stroke, with Group 1 having fewer cases than Groups 2 and 3. Vascular disease also showed significant variation, with the lowest prevalence in Group 1 and the highest in Group 3 ($P < 0.001$).

While hemoglobin levels did not differ significantly across the groups, glucose levels exhibited significant variation ($P = 0.024$), with Group 2 demonstrating the highest mean glucose level. Similarly, creatinine levels differed significantly ($P = 0.003$). No statistically significant differences were observed in TSH levels across the groups ($P = 0.302$). Conversely, CHA2DS2-VASc scores varied considerably, with the highest levels recorded in Group 3 (Group 1 vs. Group 2, $P < 0.001$; Group 2 vs. Group 3, $P = 0.017$). Sociodemographic and clinical features of the patients are presented in Table 1.

Anxiety and Depression Levels of the Patients

The analysis of anxiety and depression levels among the three patient groups revealed significant differences ($P < 0.001$). Patients' BAI scores differed significantly across groups, with Group 3 having the highest mean score (27.8 ± 12.1; $P < 0.001$). No difference was found between Group 1 and Group 2 ($P = 0.889$). Additionally, the distribution of anxiety severity varied notably among the groups. A larger proportion of Group 3 patients (87.1%) experienced moderate to severe anxiety, compared to 55.6% in Group 2 and 60.9% in Group 1.

Similarly, BDI scores were highest in Group 3 (30.1 ± 9.2), followed by Group 1 (21.8 ± 10.3) and Group 2 (25.8 ± 11.4), demonstrating statistically significant differences. However,

Table 1. Demographic and clinical characteristics of the patients

Variable	Not using anticoagulant (Group 1)	Using NOACs (Group 2)	Using warfarin (Group 3)	P
Age (years), mean ± SD	53 ± 18[a]	69 ± 11[b]	70 ± 10[b]	**<0.001**
	n (%)	**n (%)**	**n (%)**	
Gender				0.394
Female	35 (50.7)	61 (49.2)	37 (59.7)	
Male	34 (49.3)	63 (50.8)	25 (40.3)	
Education				0.161
Primary	33 (47.8)	68 (54.8)	33 (53.2)	
High school	29 (42.0)	32 (25.8)	20 (32.3)	
University	7 (10.1)	24 (19.4)	9 (14.5)	
Marital status				0.604
Married	60 (87.0)	105 (84.7)	50 (80.6)	
Single/widowed	9 (13.0)	19 (15.3)	12 (19.4)	
Age group				**<0.001**
< 65 years	55 (79.7)[a]	40 (32.3)[b]	15 (24.2)[b]	
65–75 years	14 (20.3)[a]	49 (39.5)[b]	28 (45.2)[b]	
> 75 years	0 (0)[a]	35 (28.2)[b]	19 (30.8)[b]	
Heart failure				0.335
No	65 (94.2)	110 (88.7)	54 (87.1)	
Yes	4 (5.8)	14 (11.3)	8 (12.9)	
Hypertension				**<0.001**
No	49 (71.0)[a]	37 (29.8)[b]	11 (17.7)[b]	
Yes	20 (29.0)[a]	87 (70.2)[b]	51 (82.3)[b]	
Diabetes mellitus				**0.017**
No	60 (87.0)[a]	86 (69.4)[b]	43 (69.4)[b]	
Yes	9 (13.0)[a]	38 (30.6)[b]	19 (23.6)[b]	
Stroke				**0.008**
No	69 (100.0)[a]	108 (87.1)[b]	57 (91.9)[b]	
Yes	0 (0)[a]	16 (12.9)[b]	5 (8.1)[b]	
Vascular disease				**<0.001**
No	55 (79.7)[a]	65 (52.8)[b]	18 (29)[c]	
Yes	14 (20.3)[a]	59 (47.2)[b]	44 (71.0)[c]	
	Mean ± SD	**Mean ± SD**	**Mean ± SD**	
Ejection fraction (%)	60 ± 2.5a	55 ± 10[b]	55 ± 10b	**0.009**
Hemoglobin (g/dL)	14.1 ± 2.4	13.6 ± 2.3	13.3 ± 2.2	0.521
Glucose (mg/dL)	94 ± 46[a]	103.5 ± 34.5[b]	98 ± 41[a]	**0.024**
Creatinine (mg/dL)	0.79 ± 0.17[a]	0.88 ± 0.4[b]	0.93 ± 0.3[b]	**0.003**
Thyroid-stimulating hormone (mg/dL)	0.965 ± 1.5	1.12 ± 1.3	1.23 ± 0.4	0.302
CHA2DS2-VASc	1.3 ± **0.8**[a]	3.3 ± 1.0b	3.7 ± **1.2**[c]	**<0.001**
CRP	0.3 ± 0.39	0.3 ± 0.4	0.3 ± 0.4	0.164

*Groups with different superscript letters (e.g., a, b, c) indicate statistically significant differences (P < 0.05). NOACs, Novel oral anticoagulants; SD, Standard deviation; CRP, C-reactive protein.

no substantial difference was observed between Group 1 and Group 2 (P = 0.102). Regarding depression severity, Group 3 once again showed a higher proportion of patients with moderate to very severe depression (85.5%) compared to Group 1 (59.4%) and Group 2 (65.3%). Conversely, the proportion of patients with none/very mild to mild depression was lowest in Group 3 (14.5%), compared with 40.6% in Group 1 and 34.7% in Group 2.

Table 2. Anxiety and depression levels of the patients

Variable	Not using anticoagulant (Group 1)	Using NOACs (Group 2)	Using warfarin (Group 3)	P
Beck anxiety score (mean ± SD)	19.4 ± 9.6[a]	20.1± 9.5[a]	27.8 ± 12.1[b]	<0.001
Anxiety severity, n (%)				<0.001
Minimal to mild	27[a] (39.1)	55[a] (44.4)	8[b] (12.9)	
Moderate to severe	42[a] (60.9)	69[a] (55.6)	54[b] (87.1)	
Beck depression score (mean ± SD)	21.8 ± 10.3[a]	25.8 ± 11.4[a]	30.1 ± 9.2[b]	<0.001
Depression severity, n (%)				<0.001
None/minimal to mild	28[a] (40.6)	43[a] (34.7)	9[b] (14.5)	
Moderate to very severe	41 (59.4)[a]	81 (65.3)[a]	53 (85.5)[b]	

*Variables are summarized as mean ± SD. Groups with different superscript letters (e.g., a, b) indicate statistically significant differences (P < 0.05).

These findings indicate that individuals on warfarin (Group 3) are more prone to elevated levels of anxiety and depression than those on NOACs (Group 2) or those not receiving anticoagulant treatment (Group 1). Table 2 presents a comprehensive comparison of anxiety and depression levels.

Correlation Between Depression and Anxiety Scores and Patient Characteristics

Correlation analysis was conducted to examine the relationship between participants' clinical variables and anxiety and depression levels (Table 3).

A positive correlation was found between anxiety and age scores (P = 0.034), depression scores (P < 0.001), creatinine levels (P = 0.021) and CHA2DS2-VASc score (P = 0.008), while a negative correlation was observed with ejection fraction (EF) (P < 0.001).

On the other hand, a positive correlation was found between depression scores and age (P = 0.034), anxiety scores (P < 0.001), CRP levels (P = 0.044), and CHA2DS2-VASc scores (P = 0.001).

Predictors of Anxiety and Depression

The multiple logistic regression results indicated that moderate and severe anxiety were predicted by warfarin use (odds ratio [OR]: 4.902; 95% confidence interval [CI] [1.928–12.461]; P = 0.001), EF (OR: 0.892; 95% CI [0.846–0.941]; P < 0.001), depression score (OR: 1.105; 95% CI [1.069–1.144]; P < 0.001), and CHA2DS2-VASc score (OR: 0.691; 95% CI [0.538–0.883]; P = 0.004). Depression was predicted solely by anxiety scores (OR: 1.126; 95% CI [1.081–1.173]; P < 0.001), with no other variables identified as significant predictors. The predictors determined for the variable of anxiety are presented in Table 4.

Discussion

This study investigates the prevalence of depression and anxiety in patients with NVAF and examines the relationship between these psychological conditions and the treatment regimens administered. AF predominantly affects the elderly population. In Australia, North America, and Western Europe, 70% of AF patients are over the age of 65,[21,22] and OAC therapy remains the most effective therapeutic approach for managing the condition.[14] In the present study, the mean age of AF patients was 64.08 ± 13.52 years, with 72.9% receiving oral anticoagulant therapy. It was observed that patients with higher mean age and CHA_2DS_2-VASc scores were more likely to use warfarin compared with other groups. Despite having similar efficacy and fewer side effects, warfarin was preferred over NOACs in elderly patients. This could be attributed to the relatively recent introduction of NOACs in our country[23] and/or patients' reluctance to switch from their established treatment.

The literature suggests that anxiety and depression are frequently observed in AF patients, contributing to disease progression, exacerbating symptoms, increasing the frequency of attacks, and worsening prognosis.[24-28] For instance, in a study by Thrall et al.,[29] more than one-third of AF patients were found to experience depression and anxiety. Similarly, Polikandrioti et al.[30] reported that 47.5% of AF patients exhibited anxiety symptoms, while 29.5% had depressive symptoms. Our study also revealed a high prevalence of depression and anxiety among patients. When considering moderate or higher severity cases, 68.6% met the diagnostic criteria for depression, while 64.7% met the criteria for anxiety disorder. Although these rates appear higher than those reported in previous studies, this discrepancy could be attributed to variations in the assessment scales used, cut-off values for symptom severity, sample characteristics (e.g., factors influencing psychiatric disease development such as age, gender, education level, and economic status), and cultural differences in reporting psychiatric symptoms. While our study was not designed to establish causality, it is noteworthy given the well-documented association between psychiatric comorbidities, poor prognosis, and increased mortality risk.

Previous studies have highlighted the significance of demographic variables such as age, gender, family history, and marital status in the onset and progression of psychiatric disorders.[31-33] Particularly, 10–15% of the elderly population experience clinically significant depressive symptoms that negatively impact their quality of life, with even higher rates reported among individuals with chronic illnesses.[34] Among the factors investigated in our study, age was found to be the most important demographic factor linked to increased psychiatric symptom severity; both depression and anxiety scores rose with older age. The association observed in our study aligns with earlier studies indicating that older adults could be more psychologically vulnerable.[34,35] Psychosocial stressors that frequently accompany aging could also contribute to this vulnerability, in addition to physical decline. The greater emotional burden observed in older adults may be influenced by factors such as grief, declining social support systems, transition to institutional living conditions, and perceived loss of autonomy. Furthermore, in this age group, depressive symptoms

Table 3. Correlation between anxiety and depression scores and patient characteristics

	Age	Anxiety	Depression	EF	HGB	Glucose	Creatinine	CRP	TSH	CHA_2DS_2-VASc
Age										
r	1.000	0.133*	0.133*	-0.247**	-0.224**	0.095	0.308**	-0.0061	-0.058	0.644**
P	–	**0.034**	**0.034**	**<0.001**	**<0.001**	0.132	**<0.001**	0.400	0.450	**<0.001**
Anxiety										
r	0.133*	1.000	0.430**	-0.325**	0.066	-0.008	0.145*	0.077	-0.029	0.165**
P	**0.034**	–	**<0.001**	**<0.001**	0.296	0.895	**0.021**	0.287	0.706	**0.008**
Depression										
r	0.133*	0.430**	1.000	-0.032	-0.002	-0.031	0.090	0.145*	0.050	0.204**
P	**0.034**	**<0.001**	–	0.616	0.970	0.625	0.152	**0.044**	0.510	**0.001**
EF										
r	-0.247**	-0.325**	-0.032	1.000	-0.146*	-0.128*	-0.324**	-0.169*	-0.115	-0.295**
P	**<0.001**	**<0.001**	0.616	-	**0.022**	**0.043**	**<0.001**	**0.021**	0.137	**<0.001**
HGB										
r	-0.224**	0.066	-0.002	-0.146*	1.000	0.053	0.144*	0.257**	-0.036	-0.193**
P	**<0.001**	0.296	0.970	0.022	–	0.397	0.021	**<0.001**	0.635	0.002
Glucose										
r	0.095	-0.008	-0.031	-0.128*	0.053	1.000	0.184**	0.090	0.030	0.273**
P	0.132	0.895	0.625	0.043	0.397	–	0.003	0.213	0.697	**<0.001**
Creatinine										
r	0.308**	0.145*	0.090	-0.324**	0.144*	0.184**	1.000	0.254**	0.059	0.236**
P	**<0.001**	0.021	0.152	**<0.001**	0.021	0.003	–	**<0.001**	0.437	**<0.001**
CRP										
r	-0.061	0.077	0.145*	-0.169*	0.257**	0.090	0.254**	1.000	-0.103	0.082
P	0.400	0.287	**0.044**	0.021	**<0.001**	0.213	**<0.001**	–	0.236	0.254
TSH										
r	-0.058	-0.029	0.050	-0.115	-0.036	0.030	0.059	-0.103	1.000	0.120
P	0.450	0.706	0.510	0.137	0.635	0.697	0.437	0.236	–	0.115
CHA_2DS_2-VASc										
r	0.644**	0.165**	0.204**	-0.295**	-0.193**	0.273**	0.236**	0.082	0.120	1.000
P	**<0.001**	**0.008**	**0.001**	**<0.001**	0.002	**<0.001**	**<0.001**	0.254	0.115	–

*P < 0.05, **P < 0.01. EF, Ejection fraction; HGB, Hemoglobin; CRP, C-reactive protein; TSH, Thyroid-stimulating hormone.

may sometimes manifest atypically through somatic complaints such as fatigue, pain, or cognitive decline, which could lead to underdiagnosis or misdiagnosis of underlying depression. As a result, mental health assessments in the elderly, especially those with comorbid chronic diseases, may have to be conducted using more sensitive and age-specific screening tools. Developing screening and intervention strategies that address both the biological and psychosocial aspects of mental health in the aging population may help reduce the negative impact of psychiatric symptoms on their quality of life in future research.

Table 4. Results of logistic regression analysis of anxiety

Variables	OR	95% CI	P
Depression score	1.105	1.069-1.144	<0.001
Warfarin use	4.902	1.928-12.461	0.001
EF	0.892	0.846-0.941	<0.001
CHA_2DS_2-VASc score	0.691	0.538-0.883	0.004

OR, Odd ratios; CI, Confidence interval; EF, Ejection fraction.

Consistent with prior research demonstrating that disease severity exacerbates anxiety and depressive symptoms,[36] our study found that higher CHA_2DS_2-VASc scores were associated with increased depression and anxiety scores. Moreover, the CHA_2DS_2-VASc score emerged as one of the most significant independent predictors of anxiety severity. Given that this classification includes variables such as congestive heart failure (CHF), hypertension, DM, and advanced age—all of which are individually linked to psychological distress—the observed association between elevated CHA_2DS_2-VASc scores and higher psychiatric symptomatology is not unexpected. Notably, DM has been shown to double the risk of depression,[37] likely due to mechanisms involving chronic inflammation, oxidative stress, and vascular changes affecting the brain. Similarly, hypertension

has been strongly associated with increased psychological burden; studies report that up to 56% of hypertensive individuals experience anxiety, and approximately 20% exhibit clinically significant stress symptoms.[38] Therefore, the co-occurrence of these risk factors not only exacerbates disease severity but may also contribute to a diminished ability to cope with stress.[39] Furthermore, our study revealed a positive correlation between CRP levels and depression scores, supporting the hypothesis that proinflammatory cytokines—upregulated in response to stress—contribute to depressive symptoms via neuroendocrine and neurotransmitter dysregulation.[40]

Recent literature indicates that the management of AF extends beyond pathophysiological factors, highlighting the significant impact of therapeutic strategies on patients' psychological well-being and overall quality of life. For instance, Sang et al.[41] reported that implementing catheter ablation and avoiding warfarin therapy contributed substantially to improvements in depression, anxiety, and quality-of-life measures. Similarly, a study by Altiok et al.[42] found that individuals with atrial fibrillation experienced considerable limitations in daily activities and social lives due to disease-related symptoms and the burden of warfarin treatment. Moreover, more than half of the patients reported persistent anxiety stemming from fears of palpitations, gastrointestinal bleeding, or cerebral hemorrhage as potential medication side effects. Additionally, it has been demonstrated that patients capable of managing their oral anticoagulant therapy independently report higher levels of treatment satisfaction and perceive fewer daily challenges, social burdens, and treatment-related stressors.[43] Okumura et al.[8] reported that patients using NOACs experienced greater treatment satisfaction compared to those on warfarin, while Türker et al.[9] observed a significant reduction in depression scores among patients who transitioned from warfarin to dabigatran.

The findings of the present study are consistent with previous research, indicating that patients receiving warfarin therapy exhibited significantly higher depression and anxiety scores compared to the other two groups. Furthermore, warfarin use emerged as the strongest predictor of anxiety development. Although this study was not specifically designed to examine causal relationships, it is plausible that challenges inherent to warfarin therapy, such as frequent monitoring, dietary restrictions, and bleeding risk, may have contributed to these psychological outcomes. The need for frequent blood testing, strict dietary restrictions, and persistent concerns about complications such as bleeding or embolism may contribute to heightened anxiety levels among patients receiving warfarin therapy. Additionally, the necessity for regular medical check-ups and repeated visits to healthcare facilities may impose financial burdens and contribute to a loss of productivity over time, further exacerbating depressive symptoms. Moreover, the higher CHA_2DS_2-VASc scores observed in the warfarin group indicate that these patients represent a clinically higher-risk population. This suggests that the severity of psychological symptoms in this group may be influenced not only by the demands of the treatment regimen itself but also by the broader burden of the underlying disease. In contrast, NOACs may have a more favorable impact on psychological well-being, owing to their practical advantages, such as ease of administration, lack of need for frequent INR monitoring, comparable efficacy to warfarin, and lower risk of bleeding.[44] Given that comorbid anxiety and depression can negatively affect clinical outcomes, the present findings are clinically meaningful in suggesting that NOAC use may offer psychological as well as physiological benefits for patients.

Limitations

The findings from this study provide important insights into the potential effects of anticoagulant agents used for AF treatment on patients' psychological status; however, they should be interpreted cautiously in light of several limitations. First, the study utilized a single-center sample, which limits the generalizability of the findings to broader patient populations with diverse geographic, socioeconomic, and cultural characteristics. Second, the cross-sectional design precludes the ability to draw causal inferences. In particular, because patients' psychological status prior to initiating oral anticoagulant therapy was not assessed, it is unclear whether the observed levels of depression and anxiety are attributable to the treatment itself or to pre-existing psychiatric conditions. Third, key confounding variables such as socioeconomic status, psychiatric history, health literacy, and social support were not controlled for. Given their known influence on mental health, the absence of these factors may introduce uncertainty in interpreting the results. Fourth, the study did not evaluate NOACs by individual subgroups (e.g., dabigatran, rivaroxaban, apixaban), thereby overlooking potential pharmacokinetic and side-effect differences that could differentially impact psychological outcomes. Finally, it is important to consider that some patients in the NOAC group may have previously been treated with warfarin. A transition to NOAC therapy following negative experiences with warfarin could have positively biased patients' perceptions of the new treatment and their psychological responses, potentially leading to an overestimation of the benefits associated with NOACs.

Despite these constraints, the study employed validated scales to assess depression and anxiety, and the sample size was adequate for the analyses conducted. To the best of our knowledge, this is among the first studies to compare the psychological status of patients with non-valvular atrial fibrillation who are receiving anticoagulant therapy versus those who are not. As such, it provides preliminary data that may inform and guide future research in this important area.

Conclusion

This study demonstrated a high prevalence of anxiety and depression among patients with NVAF, with psychiatric symptoms particularly pronounced in those receiving warfarin therapy. The findings suggest that the type of anticoagulant therapy may significantly affect psychological status and that NOACs are better tolerated psychologically. Additionally, factors such as age, disease severity, and inflammatory response are also thought to mediate this relationship. Therefore, in the management of NVAF, attention to patients' mental health through routine psychological assessment, patient education, and psychiatric support when needed may provide significant benefits for prognosis and quality of life. A holistic, multidisciplinary approach that integrates both cardiovascular and psychological care is recommended.

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