

# Evaluation of Depression and Anxiety Levels and Quality of Life in Patients Using Warfarin or New Oral Anticoagulants Due to Prophylaxis of Stroke

İnme Profilaksisi Nedenli Varfarin ya da Yeni Oral Antikoagulan Kullanan Hastalarda Depresyon Anksiyete ve Yaşam Kalitesi Arasındaki İlişkinin Değerlendirilmesi

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## Abstract

- Aim** In this study, we aimed to evaluate depression, anxiety and quality of life in patients who had a cardioembolic stroke history or cardioembolic stroke risk and used warfarin or new oral anticoagulants (NOAC) for prophylactic purposes. (**Sakarya Med J 2018, 8(3):568-574**)
- Methods** Our case control study included by choosing randomize total of 200 patients (n=100 for warfarin and n=100 for NOAC) in the 40-70 age group with non valvular AF who had no history of stroke but had been using warfarin or NOAC for at least 6 months for prevention of cardioembolic stroke. In addition to the sociodemographic form applied after psychiatric interviews, Beck Depression Inventory and Beck Anxiety Inventory were applied to all patients in order to determine their level of depression and anxiety and the World Health Organization Quality of Life Scale Brief Form scale was used to assess the quality of life.
- Results** Warfarin users were found to have higher depression and anxiety levels and lower level of quality of life than those of NOAC users. Furthermore there was a correlation between duration of warfarin usage and higher depression- anxiety levels and lower level of quality of life.
- Conclusion** It can be concluded that the NOAC group medicine are associated with lower depression and anxiety levels and higher quality of life compared to warfarin.
- Keywords** Anticoagulant agents; Stroke; Depression; Anxiety; Quality of life

## Öz

- Amaç** Bu çalışmada kardiyoembolik inme riski olan hastalarda profilaksi amaçlı varfarin ya da yeni oral antikoagulan (YOAK) kullanan hastalarda depresyon, anksiyete ve yaşam kalitesi düzeylerini değerlendirmeyi amaçladık. (**Sakarya Tıp Dergisi 2018, 8(3):568-574**).
- Yöntem** Vaka kontrol çalışmamıza Nisan 2016-Ağustos 2016 yılları arasında 40-70 yaş arasındaki non valvüler AF'li olan kardiyoembolik inme riski nedeniyle profilaksi amaçlı en az 6 aydır varfarin ya da YOAK kullanan toplam 200 hasta (100 varfarin, 100 YOAK) randomize seçilerek dâhil edildi. Her iki grupta belirlenen hastaların demografik özellikleri ile beraber tüm hastalarla psikiyatrik tanıları tespit etmek amaçlı psikiyatrik görüşme yapıldıktan sonra sosyodemografik formla birlikte depresyon ve anksiyete düzeyini belirlemek amaçlı Beck Depresyon Ölçeği ve Beck Anksiyete Ölçeği uygulandı. Yaşam kalitesini değerlendirme amaçlı ise Dünya Sağlık Örgütü Yaşam Kalitesi Ölçeği Kısa Formu (WHOQOL-BREF-) ölçeği uygulandı.
- Bulgular** Çalışmamızda varfarin kullananlarda depresyon ve anksiyete düzeyleri YOAK kullananlara göre yüksek bulunurken yaşam kalitesi düzeyi ise daha düşük bulunmuştur. Aynı zamanda varfarin kullanım süresi arttıkça depresyon ve anksiyete düzeylerinde artış, yaşam kalitesi düzeyinde ise azalma saptanmıştır.
- Sonuç** YOAK grubu ilaçların varfarine göre, daha düşük depresyon ve anksiyete düzeyleri ile ilişkili olduğu ayrıca YOAK grubu ilaç kullanan hastalar, daha yüksek yaşam kalitesine sahip oldukları söylenebilir.

Anahtar Kelimeler

Antikoagulan ajanlar; İnme; Depresyon; Anksiyete; Yaşam kalitesi

## Introduction

Stroke is a common health problem, causing severe morbidity, mortality and high health expenditures. Stroke is the third cause of mortality following coronary heart disease and cancers not only in developed countries, but all over the world.<sup>1,2</sup>

Atrial fibrillation (AF) is the most important and curable cardiac cause of ischemic stroke. Approximately half of cardioembolic strokes occur in patients with AF. AF independently increases the risk of stroke by 3 to 5 times. Stroke patients with AF and other cardiac problems use warfarin or new oral anticoagulants (dabigatran, rivaroxiban, apixaban) (NOAC) as a secondary protection.<sup>1-6</sup> Warfarin, an oral anticoagulant, is a vitamin K antagonist and is frequently used to prevent stroke prophylaxis and recurrence in patients with AF. Whether the serum warfarin level is in the therapeutic range is monitored by the value of international normalized ratio (INR) in the health centers. Risk of recurrent stroke increases when the INR value is below the therapeutic range and the bleeding risk increases when it's above the therapeutic range.<sup>6</sup>

Depression and anxiety disorders are the most common psychiatric disorders in the community. Stroke patients also high rate of accompanying depression and anxiety disorders. The deterioration of quality of life may depend on the development of functional disability, and also accompanying depression and anxiety may affect quality of life negatively.<sup>3-5</sup>

Patients using warfarin are followed by INR values frequently, due to its narrow therapeutic range, and interaction with food and medicine. On the other hand, there is no need to follow INR in NOACs.<sup>6,7</sup>

There are few studies in the literature evaluating depression and anxiety symptoms in patients using warfarin and NOAC.<sup>3,8,9</sup>

In this study, we aimed to evaluate depression, anxiety and quality of life in patients who had a cardioembolic stroke risk and used warfarin or NOAC for prophylactic purposes.

## Materials and Methods

**Sample:** Among the patients admitted to the neurology and cardiology outpatient clinics of Sakarya Training and Research Hospital between April and August 2016, our case control study included by choosing randomize a total of 200 patients in the 40-70 age group (n=100 for warfarin and n=100 for NOAC) with non valvular AF who had no history of stroke but had been using warfarin or NOAC for at least 6 months for prevention of cardioembolic stroke. Patients with valvular AF, stroke history, psychosis, mood disorder and dementia history, patients who suffer from substance abuse or alcohol abuse, who use psychiatric drugs for the last 6 months, who have comorbid diseases such as morbid obesity, congestive heart failure, chronic obstructive pulmonary disease and connective tissue disease and patients who have a history of stroke were excluded from the study.

Our study was approved by the Ethics Committee of Sakarya University (Ethics committee approval number: 050.01.04.58)

Patients were divided into two groups according to the use of warfarin or NOAC. Demographic characteristics such as age, gender, marital status and education level of the patients in both groups were recorded together with their chronic illnesses, drug use history and smoking habits with past stroke history. In addition to the sociodemographic form applied after psychiatric interviews, Beck Depression Inventory (BDI) and Beck Anxiety Inventory (BAI) were applied to all patients in order to determine their level of depression and anxiety. And, the World Health Organization Quality of Life Scale Brief Form (WHOQOL-BREF) scale was used to assess the quality of life.

**Beck Depression Inventory:** It's a Likert-type scale composed of 21 items developed by Beck et al.<sup>10</sup> Each item is rated between 0 and 3. Turkish validity and reliability study was conducted.<sup>11</sup>

**Beck Anxiety Inventory:** It was developed by Beck and his colleagues. It's a Likert-type scale consisting of 21 items.<sup>12</sup> Each item is rated between 0 and 3. Turkish validity and reliability study was conducted.<sup>13</sup>

**World Health Organization, Quality of Life Scale Brief Form (WHOQOL-BREF):** It was developed by the World Health Organization. This scale measures physical, mental, social and environmental well-being, and is the brief-form of the 100-item long, consisting 26 items. As each field independently expresses the quality of life in their field, the field scores are calculated between 4-20. As the score increases, the quality of life increases.<sup>14</sup> When the Turkish version (item 27 is a national question) is used, the environmental score is evaluated as environment-TR. Turkish validity and reliability study was conducted.<sup>15</sup>

**Statistical Analysis:** For the statistical analyzes, SPSS (Statistical Package for Social Sciences) for Windows 24.0 program was used. In the comparison of continuous variables, the Kolmogorov-Smirnov test was used first to test the normal distribution of the parameters. Student t test was used to compare quantitative data as well as descriptive statistical methods (Mean, Standard deviation) in evaluating the study data. Chi-square test was used for comparison of qualitative data. Pearson Correlation coefficient was used to determine whether there was a significant relationship between duration of warfarin use and BDI, BAI and WHOQOL-BREF values and linear regression analysis was performed for each of them to determine how well these values were predicted. The data were tested at a significance level of 0.05.

## Results

The mean age of warfarin users was  $54 \pm 9$ , and the mean age of NOAC users was  $53 \pm 10$ . There was no statistically significant difference between the two groups ( $p: 0.532$ ). There was no significant difference in sociodemographic and clinical characteristics in both groups. Basic demographic and clinical characteristics of both groups are shown Table 1.

Although the mean BDI and BAI for warfarin users was lower than for patients using NOAC, the WHOQOL-BREF sub-scale and total score averages were found to be high. The mean scores of BDI, BAI and WHOQOL-BREF scores in both groups are shown Table 2.

The mean duration of warfarin use was  $20 \pm 16$  months, and these patients' mean BDI score was  $19 \pm 7$ , the mean BAI score was  $16 \pm 7$ , and the mean WHOQOL BREF score was  $43 \pm 13$ . Linear

regression analysis showed that there were a 0.27 and 0.26 point increase in BDI and BAI scores, respectively for each month of warfarin use. Also, a negative 0.35 point decrease was found in the WHOQOL BREF total score, which was statistically significant. These are presented in Table 3.

**Table 1. Demographic and Clinical Characteristics of Both Groups**

	Warfarin users (N:100)	NOAC users (N:100)	p
Gender			0.203
Female	45 45%	54 54%	
Male	55 55%	46 46%	
Marital status			0.145
Single	33 33%	43 43%	
Married	67 67%	57 57%	
Education status			0.792
Literate	26 26%	30 30%	
Elementary school	46 46%	45 45%	
High school-college	28 28%	25 25%	
Smoking			0.520
No	36 36%	41 41%	
Yes	30 30%	23 23%	
Quit	34 34%	36 36%	
Hypertension	91 91%	84 84%	0.134
Diabetes	37 37%	51 51%	<b>0.046</b>
CAD	49 49%	44 44%	0.478

CAD: Coronary Artery Disease

**Table 2. BDI, BAI and WHOQOL-BREF score averages for patients using warfarin and NOAC**

	Warfarin users (N:100)	NOAC users (N:100)	p
BAI	16.7±7	8.1±4	0.00
BDI	19.2±7	8.9±4	0.00
WHOQOL BREF Physical Health	11.5±4	16.2±4	0.00
WHOQOL Mental Status	10.9±3	14.7±2	0.00
WHOQOL BREF Social Relationships	10.7±3	14.3±2	0.00
WHOQOL BREF Environmental Relationships	10.1±3	14.5±3	0.00
WHOQOL BREF Total	43.6±13	59.8±10	0.00

BAI: Beck Anxiety Inventory                      BDI: Beck Depression Inventory  
WHOQOL BREF: World Health Organization, Quality of Life Scale Brief Form  
NOAC: New Oral Anticoagulants

**Table 3. Relationship between duration of warfarin use and depression, anxiety and quality of life**

	Unstandardized B	Sig. (P value)	95.0% confidence interval for B	
			Lower Bound	Upper Bound
BDI	0.278	0.01	0.20	0.35
BAI	0.267	0.01	0.18	0.34
WHOQOL BREF Total	0.359	0.01	- 0.50	-0.21

BAI: Beck Anxiety Inventory                      BDI: Beck Depression Inventory  
WHOQOL BREF: World Health Organization, Quality of Life Scale Brief Form

**Discussion**

In our study, warfarin users were found to have higher depression and anxiety levels and lower level of quality of life than those of NOAC users. Furthermore there was a correlation between duration of warfarin usage and higher depression- anxiety levels and lower level of quality of life.

There are studies reporting that stroke deteriorates quality of life due to direct impact of disability and cognitive deterioration as well as indirect (induced by depression or anxiety) effects of change in diet and comorbid diabetes mellitus, coronary artery disease and hypertension, which play a role in the etiology of stroke.<sup>3,16</sup>

According to studies, the level of INR used to follow-up the therapeutic range of warfarin is about 60-65% even in developed countries (it is about 50% in developing countries). Factors such as diet, alcohol intake and other medications used may cause changes in INR value. 3 Cromheecke et al. and Gadisseur et al. have reported higher quality of life in patients with active INR levels.<sup>17,18</sup>

There are few studies reporting that long-term oral anticoagulant use is indirectly associated with deterioration in the quality of life due to depression and anxiety. Many of the studies reported more depressive symptoms and lower quality of life in patients using warfarin.<sup>9,19,20</sup>

In a study evaluating patients with AF using warfarin and acetyl salicylic acid, the quality of life of patients using warfarin has been found to be lower than that using acetyl salicylic acid.<sup>20</sup> Another study by Davis et al. reported decreased quality of life in approximately 19% of the patients who used warfarin for prolonged periods of time.<sup>9</sup>

A study by Turker et al., which evaluated patients in terms of depression during periods of warfarin and dabigatran use, reported a significant improvement in the depressive mood of the patients when they switched to dabigatran. Researchers have suggested that this may be due to the restriction of certain dietary products and lifestyles in order to keep INR within the therapeutic range during the warfarin use, that the frequent admission to hospitals for INR follow-up, and that the concerns about recurrent stroke or hemorrhage due to the INR outside the therapeutic range. However, it has been reported that patients with non-valvular AF who use NOAC have lower rates of admission to the hospital since they do not need INR follow-up and have lower risk of hemorrhage or anxiety of recurrent stroke.<sup>3</sup>

In studies conducted in UK, US, Canada, Sweden and Denmark comparing dabigatran and warfarin in terms of economic burden, the economic burden of patients using dabigatran was found to be

lower than those who used warfarin in the long term, probably due to their better quality of life because of the lesser risk of disability due to hemorrhage and stroke in dabigatran users.<sup>21</sup>

On the other hand, a study by Coban et al. on the quality of life of patients who use warfarin and antiplatelet therapy reported no significant difference in terms of the quality of life.<sup>4</sup> In a sub-study by Monz et al. conducted with data from a RE-LY study, where dabigatran 150 and 110 milligrams and warfarin had been compared in terms of efficacy and safety, the third month and 12th month patients have been evaluated for their quality of life. In their study, there has been no significant difference in quality of life among the patients using warfarin and dabigatran, except the group that used Dabigatran 150 mg at the 3rd month. Researchers have stated that this may be due to the quality of life scale used and the fact that stroke patients were not involved in the study.<sup>21</sup>

In our study, depression and anxiety levels of patients using NOAC were lower than those of warfarin users. The findings of our study showed that the quality of life of patients using NOAC was higher than those using warfarin.

A study conducted by Michal et al. have reported that the increase in depression and anxiety levels in patients using warfarin also increased the difficulty in holding the INR levels in the therapeutic range due to these clinical manifestations, and that increased the risk of hemorrhage or recurrent stroke paradoxically.<sup>22</sup> Two studies conducted by Turker et al. with valvular AF patients using warfarin reported that depressive mood makes it difficult to maintain effective INR levels, and that the use of NOAC may indirectly lead to more effective stroke prophylaxis due to the reduced incidence of depression and anxiety symptoms since use of NOAC does not require INR follow-up in nonvalvular AF patients.<sup>3,8</sup>

Studies also reported an increased incidence of depression as the duration of warfarin use increased.<sup>3,8,9</sup> In our study, it was found that patients who used warfarin had a higher level of depression and anxiety and a decrease in their quality of life as the duration of use increases.

There is a limitation of our study. The depression, anxiety and quality of life levels were not evaluated separately during the periods of use of warfarin and NOAC.

As a result, it can be concluded that the NOAC group medicine are associated with lower depression and anxiety levels compared to warfarin. In addition, patients using NOAC-group medicine may have higher quality of life. However, we believe that further comprehensive studies are needed to evaluate the comorbid psychiatric disorders and quality of life in patients who use warfarin and NOAC.

**Declaration of conflicting interests:** The authors declare no conflicts of interest with respect to the authorship and/or publication of this article.

**Funding:** The authors received no financial support for the research and/or authorship of this article.

**Acknowledgements:** The authors have no acknowledgements to declare.

**Ethical Standarts:** The authors declare that this article is appropriate for ethical standarts.



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