RESEARCH ARTICLE / ARAŞTIRMA MAKALESİ

Evaluation Of The Demographic Characteristics Of Patients Who Had An Ischemic Stroke While Using Non-Vitamin K Antagonist Oral Anticoagulant

Yeni Nesil Oral Antikoagülan Kullanırken İskemik İnme Geçiren Hastaların Demografik Özelliklerinin Değerlendirilmesi

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ABSTRACT

Aim: In this study, we aimed to evaluate the demographic characteristics of patients who had an ischemic stroke while using non-vitamin K antagonist oral anticoagulants (NOAC).

Materials and Methods: Patients who had an ischemic stroke while using NOACs between January 2015 and January 2020 were included in the study. Patients and their relatives were called by phone and their file records were used to obtain their age, gender, comorbidities, NOAC use, routine biochemical and haematological parameters and transthoracic echocardiography information.

Results: The study included 73 patients diagnosed with non-valvular atrial fibrillation (AF) who had a stroke while using NOACs. Of these patients, 23 (31.5%) were male and 50 (68.5%) were female. The mean age of the patients was 74.6±10 years. The mean CHA_2DS_2-VASc score was 5.6±1.5. Of the patients, 34 (46.6%) had recurrent strokes. All patients had vascular disease. Sixty-seven (91.8%) patients had hypertension. Twenty-one patients who were receiving NOACs were found to be receiving the NOACs at doses not recommended by the current guidelines. The mean age was higher and the CHA_2DS_2-VASc score was lower in patients who did not receive the appropriate dose compared to those who did receive the appropriate dose. The history of ischemic stroke was lower in patients who did not receive the

appropriate dose compared to those who did receive the appropriate dose.

Conclusion: The high CHA$_2$DS$_2$-VASc score of patients who had a stroke despite treatment with NOACs, the presence of vascular disease in all of them, the presence of hypertension in the majority and a history of ischemic stroke in almost half of these patients all suggest that NOAC treatment may be insufficient in patients with the high risk factors of vascular disease, hypertension and a history of ischemic stroke. In addition, the reasons why about one third of patients use NOACs at an insufficient dose needs to be investigated. These data should be evaluated by studies conducted with larger numbers of patients.

Keywords: Atrial fibrillation, non-vitamin K antagonist oral anticoagulant, stroke

ÖZET

Amaç: Biz bu çalışmamızda yeni nesil oral antikoagulan (YOAK) kullanırken iskemik inme geçiren atriyal fibrilasyon*lu* (AF) hastaların demografik özelliklerini değerlendirmeyi amaçladık.

Materyal ve Metod: 2015 ocak ve 2020 ocak ayları arasında YOAK kullanırken iskemik inme geçiren hastalar çalışmaya dahil edilmiştir. Hastalar ve yakınları telefonla aranarak ve dosya kayıtları üzerinden hastaların yaş, cinsiyet bilgileri, eşlik eden hastalıklar, YOAK kullanımı, rutin biyokimyasal ve hematolojik parametreler ile transtorasik ekokardiyografi bilgilerine ulaşıldı.

Bulgular: Non-valvüler AF tanılı ve yeni nesil oral antikoagulan kullanırken inme geçieren 73 kişi çalışmaya alındı. Hastaların 23'ü (% 31.5) erkek ve 50'si (% 68.5) kadın bireylerden oluşmaktaydı. Hastaların yaş ortalaması 74.6±10 yıldı. Ortalama CHA2DS2-VASc skoru 5.6±1.5 olarak bulundu. Hastaların 34 (% 46.6) tanesi tekrarlayan inmeydi. Altmış yedi (91.8%) hastanın hipertansiyonu vardı. Hastalardan 21 tanesi uygun dozda YOAK kullanmıyordu. Hastaların tamamında vasküler hastalık mevcuttu. Uygun dozda kullanmayanların uygun dozda kullananlara göre yaş ortalamasının daha yüksek olup CHA2DS2-VASc skorunun daha düşük olduğu gözlendi. Uygun dozda kullanmayanlarda uygun dozda kullananlara göre daha az iskemik inme öyküsü vardı

Sonuç: YOAK altında inme geçiren hastaların CHADS-VASc skorunun yüksek olması, tamamının vasküler hastalığı olması, büyük çoğunluğunun hipertansiyonu olması ve bu hastaların yaklaşık yarısında iskemik stroke öyküsü olması nedeniyle, YOAK tedavisi risk faktörü yüksek olan, vasküler hastalığı olan, hipertansiyonu ve iskemik stroke öyküsü olan hastalarda yetersiz kalıyor olabilir. Ayrıca artan yaşla birlikte hastaların yaklaşık üçte birinde yetersiz dozda YOAK kullanmakta olup nedenlerinin araştırılması gerekir. Bu verilerin çok sayıda hasta alınan çalışmalar ile değerlendirilmesi gerekir.

Anahtar Kelimeler: Atriyal fibrilasyon, yeni nesil oral antikoagulan, inme

Introduction

According to the World Health Organization's definition, stroke is a clinical entity characterized by sudden onset of signs and symptoms of focal cerebral function loss without

any reason other than vascular causes.[1] Approximately 87% of stroke patients are of ischemic and 13% are of haemorrhagic origin.[2] Despite advances in the treatment of acute stroke, stroke-related deaths are still ranked third in many countries.

Atrial fibrillation (AF) is an important health problem due to the increased risk of embolism and stroke. Ischemic stroke is one of the most significant complications of AF and can cause mortality and morbidity.[3] The use of CHA_2DS_2-VASc scoring is recommended for predicting the risk of stroke in patients with non-valvular AF.[4] According to this score, the presence of congestive heart failure (CHF), hypertension (HT), advanced age, diabetes mellitus (DM), female gender, history of stroke and vascular disease are used to determine the risk of stroke.[3,4,5]

In recent years, the frequency with which non-vitamin K antagonist oral anticoagulants (NOACs) are used with non-valvular AF has increased. Rivaroxaban, apixaban, edoxaban and dabigatran are all used for this purpose. Rivaroxaban, apixaban and edoxaban are direct factor Xa inhibitors, whereas dabigatran is a direct thrombin inhibitor.[6] Previous studies have shown that the use of either apixaban 5 mg 2x1 or dabigatran 150 mg 2x1 is superior to warfarin in preventing ischemic stroke and embolism.[7,8] Edoxaban and rivaroxaban have been found to have similar effects to warfarin in preventing ischemic stroke and embolism.[9,10] Studies have shown that the incidence of ischemic stroke in patients who receive NOACs is approximately 1-2%.[7,8,9,10] In this study, we aimed to evaluate the demographic characteristics of patients who had an ischemic stroke while using NOACs.

Material-Methods

Patients who had an ischemic stroke while using NOACs between January 2015 and January 2020 were included in the study. Patients and their relatives were called by phone and their file records were used to obtain their age, gender, comorbidities, NOAC use, routine biochemical and haematological parameters and transthoracic echocardiography information. Moderate-severe rheumatic mitral valve stenosis and mechanical heart valve history were considered valvular AF.[11]

The CHA_2DS_2-VASc score was used to calculate the risk of ischemic stroke in patients with

non-valvular AF. This scheme is scored by two points each for a history of stroke/transient ischemic attack (TIA) and age >75, and 1 point each for age 65–74, history of hypertension, diabetes, heart failure, vascular disease (myocardial infarction, complex aortic plaque and past revascularization, and peripheral arterial disease (PAD), including angiographic PAD findings, PAD-related amputation) and female gender. Valvular AF and inadequate file records were considered exclusion criteria. Hypertension was defined as previous documentation of a systolic blood pressure of 140 mm Hg and/or a diastolic blood pressure of 90 mm Hg in at least 2 measurements or active use of any antihypertensive agent. Diabetes mellitus was defined as a fasting plasma glucose level over 126 mg/dL, a glucose level over 200 mg/dL, a glycated haemoglobin level over 6.5% in any measurement or the active use of an antidiabetic agent. A history of percutaneous coronary intervention, a history of myocardial infarction and a history of coronary artery bypass graft were all considered to indicate the presence of coronary artery disease. Peripheral artery disease and carotid artery disease were diagnosed with Doppler ultrasonography or peripheral angiography. The study was approved by the Sakarya University Faculty of Medicine Ethics Committee (Ethics Committee number: 71522473/050.01.04/126).

Statistical analysis

Statistical analyses were conducted using SPSS Statistics for Windows, Version 17.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as mean±SD and categorical variables as percentages. The assumption of normality was tested via the Shapiro-Wilk test. Continuous variables between twogroups were evaluated using Student's t-test and categorical variables were evaluated with a chi-square test. For all tests, a p-value <0.05 was considered statistically significant.

Results

The study included 73 patients diagnosed with non-valvular AF who had a stroke while using NOACs. Of these patients, 23 (31.5%) were male and 50 (68.5%) were female. The mean age of the patients was 74.6±10 years. The demographic characteristics of the patients are shown in Table 1. The mean CHA_2DS_2-VASc score was 5.6±1.5. Patient distribution according to the CHA_2DS_2-VASc score is shown in Figure 1. Of the patients, 34 had recurrent strokes. All patients had vascular disease. Of the patients, 42 were receiving rivaroxaban, 18 were

receiving apixaban, 11 were receiving dabigatran and 2 were receiving edoxaban. The rates of NOAC types used in our region and the rates of patients who had a stroke while receiving NOACs were very similar. Twenty-one patients who were receiving NOACs were found to be receiving the NOACs at doses not recommended by the current guidelines. Table 2 shows the demographic characteristics of those who received the appropriate dose of the new generation of oral anticoagulants and those who did not. The mean age was higher and the CHA_2DS_2-VASc score was lower in patients who did not receive the appropriate dose compared to those who did receive the appropriate dose, but there was no statistically significant difference between the two groups. The history of ischemic stroke was lower in patients who did not receive the appropriate dose compared to those who did receive the appropriate dose (29 vs 5, p: 0.013)

Discussion

Atrial fibrillation is the most common type of arrhythmia in clinical practice.[12] Its incidence in the general population is 1–2%. The incidence of this arrhythmia, the prevalence of which increases with age, has increased in recent years. AF is a major risk factor for first stroke in patients who have had no previous stroke, and for recurrent strokes in patients who have suffered a TIA or stroke previously. The rate of AF detected in a 24-hour rhythm follow-up after stroke is 1.2%, whereas this rate rises to 6.2% in a 72-hour rhythm follow-up. This is quite important in terms of treatment modality and prognosis.[13] The direct contribution of anticoagulant therapy to survival when started after a stroke in patients with AF has been demonstrated. In patients with atrial fibrillation without additional therapy, post-stroke mortality was 45.2%, and this rate dropped to 18.9% in patients who did receive anticoagulant treatment.[14,15]

The prognosis for AF-related strokes is known to be worse than that of other aetiologies.[16] For this reason, there is a need to start prophylactic treatment before a major stroke or a severe disability develops in patients with AF. There is consensus regarding the application of anticoagulant therapy in patients with cardioembolic stroke unless there is a contraindication.[17]

Vitamin K antagonists (VKA) are widely used and provide effective protection in the long-term treatment of thromboembolic diseases and in the prevention of atrial fibrillation induced

stroke.[18] Since warfarin requires constant follow-up during use, it creates difficulties for patients. Difficulty in follow-up was the reason given by more than half the patients who were unable to receive or to continue to receive anticoagulants. Although warfarin is very effective when it is used within therapeutic limits, there is a need to investigate new anticoagulant therapies because of the difficulty of follow-up during use and its excessive interaction between food and medicine.

In valvular AF, VKA drugs are the only option we have. However, to prevent recurrence of stroke in non-valvular AF patients, dabigatran, apixaban, rivaroxaban, and edoxaban have been recommended based on various evidence levels, in addition to warfarin which is recommended at class 1A level.[19,6] In non-valvular AF, NOACs are as effective and promising as VKAs. NOACs are at least as effective as VKA in stroke prevention and are considered more reliable than VKAs where there are bleeding complications.[7,8,9,10]

In our study, patients diagnosed with non-valvular AF who had a stroke while using NOACs were evaluated retrospectively. It was found that the majority of non-valvular AF patients who had a stroke had multiple risk factors for the development of thromboembolic events according to current guidelines, and most patients were found to have a CHA_2DS_2-VASc score of five and above. In our findings, the risk factors associated with AF were age, HT, vascular disease, ischemic stroke and DM.

Of the patients, 21 (28.8%) were observed to use inadequate doses of drugs. Patients receiving an inappropriate dose of NOACs were found to have lower CHA_2DS_2-VASc scores and to be elderly. Although the reasons for patients receiving inadequate doses of drugs are not known, we believe it may be due to the risk of bleeding at an advanced age.

Coronary artery disease was present in 24 (44%) patients and peripheral vascular disease was present in 53 (98%) patients who had a stroke while receiving NOACs. The fact that patients with a history of vascular disease had a greater stroke incidence raised questions about whether NOACs were inadequate for the prevention of stroke in AF patients with a history of vascular disease, or whether a combination with antiaggregant treatment is necessary. We believe that these questions will be answered by further studies on this subject.

The majority of the patients had a history of hypertension. We observed that the CHA_2DS_2-VASc score was higher in patients who had a stroke while using the appropriate dose of NOACs. Similarly, approximately half the patients had a history of ischemic stroke. In addition, the efficacy of combined antiaggregant therapy in patients with a high CHA_2DS_2-VASc score, hypertension and a history of ischemic stroke should be supported by further prospective studies.

Limitations

This is a single-centred retrospective study carried out with a small number of patients. The demographic characteristics of the patients who had an ischemic stroke while receiving apixaban, edoxaban, rivaroxaban and dabigatran were not compared due to the insufficient number of patients.

Conclusion

The high CHA_2DS_2-VASc score of patients who had a stroke despite treatment with NOACs, the presence of vascular disease in all of them, the presence of hypertension in the majority and a history of ischemic stroke in almost half of these patients all suggest that NOAC treatment may be insufficient in patients with the high risk factors of vascular disease, hypertension and a history of ischemic stroke. In addition, the reasons why about one third of patients use NOACs at an insufficient dose needs to be investigated. We believe this study will be useful for physicians in the follow-up of non-valvular AF patients who present with ischemic stroke while using NOACs. These data should be evaluated by studies conducted with larger numbers of patients.

Table 1. Demographic characteristics of patients who had an ischemic stroke while using -vitamin K antagonist oral anticoagulants.

Parameter	n, (%)

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Ages (years) *	74.6±10
Gender (female), n (%)	50, (68.5)
Hypertansion, n (%)	67, (91.8)
Diabetes Mellitus, n (%)	24, (32.9)
Coronary Artery Disease, n (%)	34, (46.6)
Heart Failure, n (%)	22, (30.1)
Carotid Artery Disease, n (%)	68, (93.2)
Stroke, n (%)	34, (46.6)
Vascular Disease, n (%)	73, (100)
Chronic Kidney Disease, n (%)	8, (11.0)
CHA2DS2VASc score *	5.6±1.5
Appropriate dose, n (%)	52, (71.2)

* Mean±SD, CHA2DS2VASc: Congestive Heart failure, hypertension, Age ≥75 (doubled), Diabetes, Stroke (doubled), Vascular disease, Age 65–74, and Sex (female)

Table 2. Comparison of demographic characteristics between patients with appropriate dose and inappropriate dose.

	Appropriate dose	Inappropriate dose	p
Age, years *	73.2±11.1	78.1±5.3	NS
Gender, female, n	35	15	NS
Hypertension, n	49	18	NS
Diabetes Mellitus, n	18	6	NS
Chronic Kidney Disease, n	8	0	NS
Heart Failure, n	15	7	NS
CHA2DS2VASc *	5.8±1.6	5.6±1.7	NS
Stroke, n	29	5	0.013
Vascular Disease, n	52	21	NS

* Mean±SD, CHA2DS2VASc: Congestive Heart failure, hypertension, Age ≥75 (doubled), Diabetes, Stroke (doubled), Vascular disease, Age 65–74, and Sex (female), NS: Not significant (p>0.05)

Figure 1. Patient distribution according to the CHA_2DS_2-VASc score is shown.
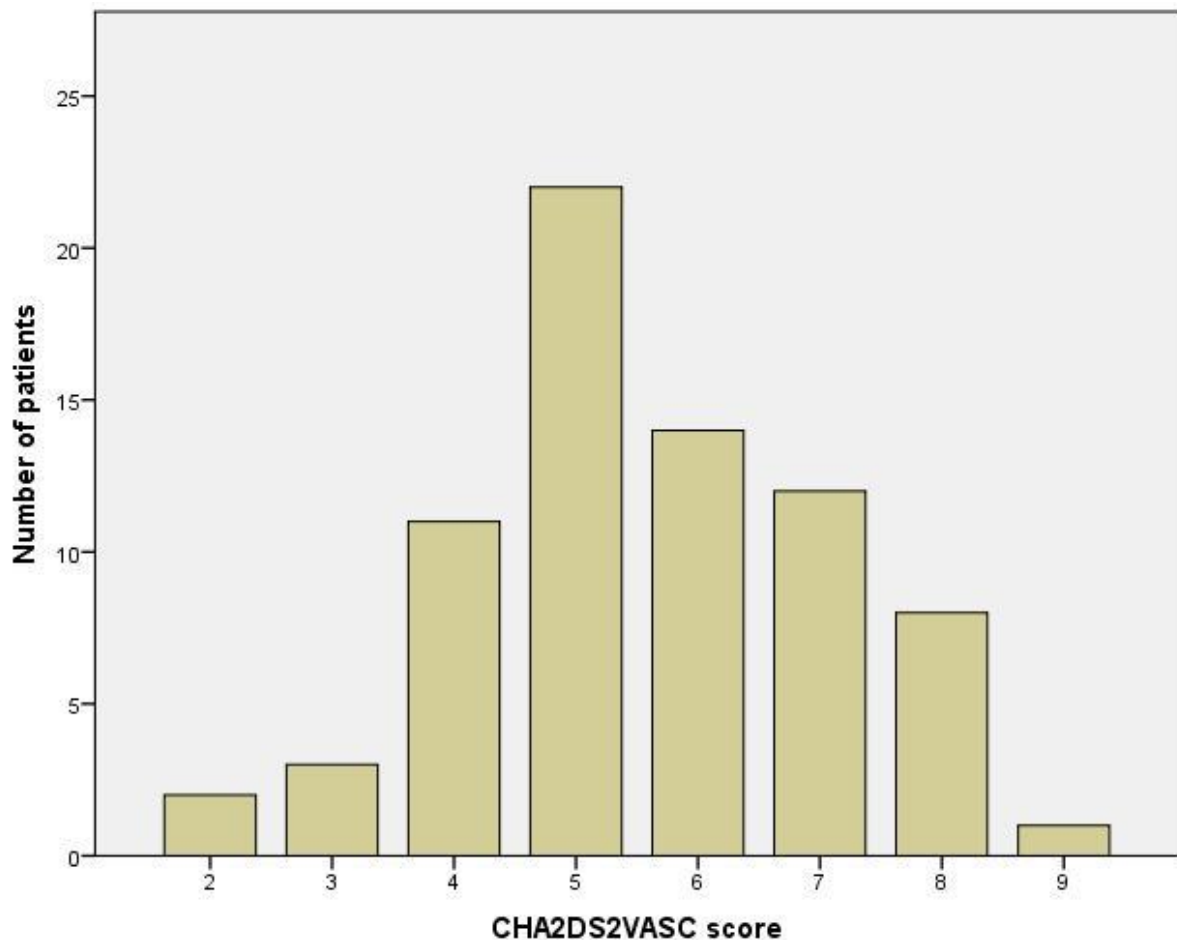
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