

Assessment of Non-Vitamin K Antagonist Oral Anticoagulant Dosing Patterns in Turkish Patients with Non-Valvular Atrial Fibrillation: A Multicenter, Cross-Sectional Study with Insights from the ASPECT-NOAC Study*

Kalp Kapak Hastalığı Olmayan Atriyal Fibrilasyonlu Türk Hastalarda Vitamin K Antagonisti Olmayan Oral Antikoagülan (NOAC) Dozlama Paternlerinin Değerlendirilmesi: ASPECT-NOAC Çalışmasından Görüşlerle Çok Merkezli, Kesitsel Bir Çalışma

ABSTRACT

Objective: We aimed to assess the real-world label adherence of non-vitamin K antagonist oral anticoagulant (NOAC) dosing patterns, including apixaban, edoxaban, and rivaroxaban, in Turkish patients with atrial fibrillation.

Methods: This was an observational, prospective, cross-sectional, multicenter study. Patients with atrial fibrillation (AF) who were prescribed NOACs within the last 4 months were recruited from 34 cardiology clinics in Türkiye. Baseline data were initially collected, and patient awareness was evaluated at 3-4 weeks.

Results: A total of 903 patients were enrolled in the study. The mean age was 72.84 ± 10.17 years. We found that 140 (15.5%), 721 (79.8%), and 42 patients (4.7%) were prescribed off-label low, on-label, and off-label high dosing, respectively. The age of the patients in the on-label group was significantly lower than that of those in the off-label low and off-label high groups (both $P < 0.001$). Female patients were more frequently observed in the off-label high group ($P = 0.019$). The body mass index values of the patients in the off-label high-dose group were significantly lower than those in the other groups ($P < 0.001$). The perception of income levels also revealed significant differences between the groups ($P = 0.010$). Furthermore, the HAS-BLED scores (the Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile International Normalized Ratio, Elderly, Drugs/Alcohol Concomitantly) were significantly lower in the on-label group than in the other groups ($P < 0.001$). Similarly, the CHA₂DS₂-VASc [the Congestive Heart Failure, Hypertension, Age ≥ 75 (Doubled), Diabetes, Stroke (Doubled), Vascular Disease, Age 65-74, and Sex Category (Female)] scores were significantly lower in the on-label group than in the off-label group ($P < 0.001$).

Conclusion: The clinical impact off-label NOAC prescriptions may vary. Therefore, raising clinician awareness about proper NOAC dosing could aid in improve the outcomes.

Keywords: Anticoagulants, atrial fibrillation, dosing pattern, non-vitamin K antagonist oral anticoagulants, patient medication knowledge

ÖZET

Amaç: Atriyal fibrilasyonu (AF) olan Türk hastalarda apixaban, edoksaban ve rivaroksaban dahil olmak üzere K vitamini antagonisti olmayan oral antikoagülan (NOAK) doz paternlerinin gerçek dünyadaki etiket uyumunu değerlendirmeyi amaçladık.

Yöntem: Bu çalışma gözlemsel, prospektif, çok merkezli bir çalışmadır. Türkiye'deki 34 kardiyoloji kliniğinden son 4 ay içinde NOAK reçete edilen AF'li hastalar çalışmaya alındı. Başlangıç verileri başlangıçta toplandı ve hasta farkındalığı 3.-4. haftada değerlendirildi.

Bulgular: Çalışmaya toplam 903 hasta dahil edildi. Yaş ortalaması $72,84 \pm 10,17$ idi. Çalışmada; 140 (%15,5), 721 (%79,8) ve 42 hastaya (%4,7) sırasıyla endikasyon dışı düşük, endikasyon dahilinde ve endikasyon dışı yüksek doz reçete edildiğini bulduk. Endikasyonu olan gruptaki hastaların yaşı, endikasyon dışı düşük ve endikasyon dışı yüksek gruptakilere göre anlamlı olarak

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Özer Badak¹ 

Demet Özkaramanlı Gür² 

Çağlar Kaya³ 

Tugay Önal⁴ 

Onur Saydam⁴ 

İbrahim Faruk Aktürk⁵ 

Servet Altay³

Ahmet Altuğ Çinçin⁶ 

Refik Emre Altekin⁷ 

Göksel Çağırıcı⁸ 

Kadriye Kılıçkesmez⁹ 

Veli Polat⁵ 

Dursun Aras¹⁰ 

¹Department of Cardiology, Dokuz Eylül University, Faculty of Medicine, İzmir, Türkiye

²Department of Cardiology, Namık Kemal University Health Application and Research Hospital, Tekirdağ, Türkiye

³Department of Cardiology, Trakya University Health Research and Application Center, Edirne, Türkiye

⁴Medical Department of Internal Medicine, Pfizer, İstanbul, Türkiye

⁵Department of Cardiology, Bakırköy Dr. Sadi Konuk Training and Research Hospital, İstanbul, Türkiye

⁶Department of Cardiology, Marmara University Pendik Training and Research Hospital, İstanbul, Türkiye

⁷Department of Cardiology, Akdeniz University Hospital, Antalya, Türkiye

⁸Department of Cardiology, Antalya Training and Research Hospital, Antalya, Türkiye

⁹Department of Cardiology, Şişli Hamidiye Etfal Training and Research Hospital, İstanbul, Türkiye

¹⁰Department of Cardiology, İstanbul Medipol University Bahçelievler Hospital, İstanbul, Türkiye

Corresponding author:

Onur Saydam

✉ onur.saydam@pfizer.com

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daha düşüktü (her ikisi de $P < 0,001$). Kadın hastalar endikasyon dışı yüksek grupta daha sık gözlendi ($P = 0,019$). Endikasyon dışı düşük ve endikasyon dahilinde reçete edilen gruplardaki hastalar endikasyon dışı yüksek reçete edilen grupla karşılaştırıldığında anlamlı ölçüde daha obezdi ($P < 0,001$). Gelir düzeyi algısı da gruplar arasında anlamlı farklılıklar olduğunu ortaya koydu ($P = 0,010$). Ayrıca, HAS-BLED skorları endikasyon dahilinde reçetelenen grupta diğer gruplara göre anlamlı olarak daha düşüktü ($P < 0,001$). Benzer şekilde, CHA2DS2-VASc skorları etiket üstü grupta etiket dışı gruba göre anlamlı olarak daha düşüktü ($P < 0,001$).

Sonuç: Endikasyon dışı NOAK reçetelerinin klinik etkisi değişiklik gösterir. Bu nedenle, uygun NOAK dozlaması hakkında klinisyen farkındalığının artırılması, sonuçların iyileştirilmesine yardımcı olabilir.

Anahtar Kelimeler: Antikoagülanlar, atriyal fibrilasyon, dozlama paterni, K vitamini antagonisti olmayan oral antikoagülanlar, hastanın ilaç bilgisi

Direct-acting oral anticoagulants known as non-vitamin K antagonist oral anticoagulants (NOACs) have been used for years to prevent ischemic stroke (IS) and systemic embolism (SE) in patients with non-valvular atrial fibrillation (NVAF).¹ Apixaban, rivaroxaban, and edoxaban are direct oral factor Xa inhibitors, whereas dabigatran is a direct thrombin inhibitor.²

Following the approval of dabigatran in 2010, the Food and Drug Administration (FDA) also approved the clinical use of apixaban, edoxaban, and rivaroxaban.^{3,4} In fact, NOACs have been prescribed more frequently than warfarin due to the need for less frequent follow-ups and fewer drug-food interactions.⁵

NOACs are associated with a similar or lower risk of IS and SE compared to warfarin; however, the high prescription rates of inappropriate dosages of NOACs remain a vital clinical problem that needs to be addressed to ensure the efficacy and safety outcomes of the treatment.^{6,7}

The inappropriate use of low-dose NOACs has been reported in many geographic areas and countries, including the United States, Asia, and Taiwan.^{8–10} Additionally, off-label low NOAC dosing has been associated with poor clinical outcomes, based on the findings of several studies.^{11–13} Unlike warfarin, it is not necessary to monitor the drug concentration of NOACs, with few exceptions; therefore, limited real-world data are available on the actual percentages of inappropriate use and their relationship to clinical outcomes.¹⁴ Thus, dosing patterns and the consequences of off-label NOAC use remain controversial.

In this study, we assessed the dosing patterns of apixaban, edoxaban, and rivaroxaban with real-world labeling data in Turkish community practice.

ABBREVIATIONS

AF	Atrial fibrillation
ANOVA	Analysis of Variance
BMI	Body mass index
FDA	Food and Drug Administration
GFR	Glomerular filtration rate
IS	Ischemic stroke
JAKQ	Jessa Atrial Fibrillation Knowledge Questionnaire
MB	Major bleeding
NOAC	Non-vitamin K antagonist oral anticoagulant
NVAF	Non-valvular atrial fibrillation
SE	Systemic embolism
OAC	Oral anticoagulant
OFHD	Off-label high dosing
OFLD	Off-label low dosing
OL	On-Label

Materials and Methods

Study Design and Patients

This study was a secondary cross-sectional subgroup analysis of the ASPECT-NOAC trial (Anticoagulation and Stroke Prevention Expert Consensus for Non-Vitamin K Antagonist Oral Anticoagulants), which was designed as a multicenter, prospective, observational study.¹⁵ Patients with NVAF were recruited from 34 cardiology clinics across all geographic regions of Türkiye. Patient enrollment took place from January 2018 to December 2018. This subgroup analysis covered adult NVAF patients (aged 18 years or older) who were currently undergoing NOAC treatment (apixaban, rivaroxaban, or edoxaban, excluding dabigatran) initiated within the previous 4 months. Since the 150 mg and 110 mg twice daily (BID) doses of dabigatran were considered appropriate (which were included in the primary analysis), they were excluded from this analysis.¹⁶ Other exclusion criteria included cognitive impairment as assessed by the attending investigator, and participation in another study within the last 6 months. The study design was approved by the Dokuz Eylül University Clinical Trials Ethics Committee of the coordinating study site (Approval Number: 2917/20-04, Date: November 30, 2017). All patients were informed about the study and provided written informed consent before participating in any study-related activities.

Table 1 shows the criteria for the dosage adjustment for the three NOACs. The on-label dose (OL) was defined based on the dosage recommendation criteria of the approved label, which is developed in line with NOAC randomized studies and International Society guidelines recommendations.^{17–23} Any lower or higher dosage or daily dose regimen was considered off-label low dosing (OFLD) and off-label high dosing (OFHD).

Data Collection

The study was conducted in accordance with the Declaration of Helsinki. Baseline demographics, clinical and medication history, and the presence of risk factors were collected via an electronic case report form at initial enrollment (baseline visit). Baseline CHA2DS2-VASc (congestive heart failure or left ventricular dysfunction, hypertension, age 65–75 years, diabetes mellitus, vascular disease, female sex [1 point for presence of each], thromboembolism or stroke history, age ≥ 75 years [2 points for presence of each]) and HAS-BLED (hypertension, abnormal renal function, abnormal liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly [age > 65 years], drugs predisposing to bleed, alcohol use [1 point for presence of each]) scores were calculated to assess the risks of

stroke and major bleeding (MB), respectively.¹⁷ Furthermore, the appropriateness of the daily NOAC doses for each patient was determined using the dose-modification criteria stated in the approved summaries of NOAC product characteristics (SmPC).²¹⁻²³

Patient awareness of atrial fibrillation (AF) and NOAC treatment was measured using the modified Jessa Atrial Fibrillation Knowledge Questionnaire (JAKQ), and the percentage of correct answers was calculated separately for AF and NOAC treatments. The JAKQ covers crucial elements of AF management and oral anticoagulant (OAC) therapy. It encompasses both theoretical questions and practical ones related to self-management behaviors such as pulse measurements, maintaining a healthy lifestyle, and appropriate actions in specific situations. Given that preventing thromboembolic stroke is a primary goal in AF management, the JAKQ dedicates half its content to OAC therapy, addressing potential side effects, the use of additional medications, self-care, and the importance of adherence.²⁴

Objective

The primary aim of this study was to evaluate the compliance of apixaban, edoxaban, and rivaroxaban doses with real-world labeling and the clinical outcomes in Turkish community practice. The secondary aim was to evaluate the knowledge level of AF and NOAC according to dosing patterns.

Statistical Analyses

We performed normality tests of numerical variables using the Shapiro-Wilk test. Descriptive statistics of these variables are presented as mean ± standard deviation (SD), while categorical variables are expressed as numbers and percentages. Moreover, the Chi-square test was used to compare nominal data. Patient knowledge levels were evaluated for sex, education level, and income level subgroups, while correlation analyses were performed for age and body mass index (BMI). We used the independent samples t-test or Mann-Whitney U test for the comparison of two independent groups, as appropriate. For the comparison of multiple groups, Kruskal-Wallis or Analysis

of Variance (ANOVA) tests were used, where appropriate. Furthermore, the Mann-Whitney U test with Bonferroni correction was used for post-hoc analysis of the Kruskal-Wallis test, while Tukey’s test was used for post-hoc analysis of the ANOVA test. Statistical calculations and the effect size were calculated as Cohen’s d. SPSS (IBM SPSS version 23, Armonk, N.Y., USA) and Jamovi (The Jamovi project, Jamovi version 1.0.8, Sydney, Australia,) were used for statistical analysis. The significance level (p-value) was set at 0.05, and the Bonferroni adjustment was applied in the post-hoc tests. No artificial intelligence tools such as Large Language Models (LLMs), chatbots, or image creators were used.

Results

A total of 903 patients were enrolled in this study. We found that 140 (15.5%), 721 (79.8%), and 42 patients (4.7%) were prescribed off-label low, on-label, and off-label high dosing, respectively. The demographic and clinical characteristics of the study groups are presented in Table 2. We detected significant differences in age, sex distribution, BMI, and perception of income level between the dosing pattern groups (*P* < 0.05). The age of patients in the OL group (68.1 ± 9.8 years) was significantly lower than those in the OFLD (74.2 ± 9.6 years) and OFHD (73.4 ± 12.1 years) (both *P* < 0.001). Additionally, the proportion of female patients in the OFHD group was significantly higher than that in the other groups (*n* = 29/42 (69.1%) vs. *n* = 63/140 (45.0%), and *n* = 383/721 (53.1%), *P* = 0.019). In contrast, the BMI values of the patients in the OFHD group were significantly lower than those in the other groups (*P* < 0.001). The perception of income levels also revealed significant differences between the groups (*P* = 0.010) (Table 2). However, other demographic and clinical characteristics did not show statistically significant differences (*P* > 0.05).

Regarding the HAS-BLED and CHA2DS2-VASc scores, these differed significantly between the groups (*P* < 0.05) (Table 2). The HAS-BLED scores in the OL group were significantly lower

Table 1. Eligibility and Dosage Adjustment Criteria for Non-Vitamin K Antagonist Oral Anticoagulant

Drug	On-label Dosing	Low Off-label Dosing	High Off-label Dosing
Rivaroxaban	Rivaroxaban 20 mg QD if CCr ≥ 50 mL/min OR Rivaroxaban 15 mg QD if CCr < 50 mL/min	Less than 20 mg QD if CCr ≥ 50 mL/min OR Less than 15 mg QD if CCr < 50 mL/min	More than 20 mg QD if CCr ≥ 50 mL/min OR More than 15 mg QD if CCr < 50 mL/min
Apixaban	Apixaban 2.5 mg BID if ≥ 2 of the following criteria are met: Age ≥ 80 years; serum creatinine ≥ 1.5 mg/dL; Body weight ≤ 60 kg OR Apixaban 2.5 mg BID if CCr 15-30 mL/min OR Apixaban 5 mg BID if none of the dosage reduction criteria are met	Less than 2.5 mg BID if dosage reduction criteria are met OR Less than 2.5 mg BID if CCr 15-30 mL/min OR Less than 5 mg BID if dosage reduction criteria are not met	More than 2.5 mg BID if dosage reduction criteria are met OR More than 2.5 mg BID if CCr 15-30 mL/min OR More than 5 mg BID if dosage reduction criteria are not met
Edoxaban	Edoxaban 30 mg QD if any of the following criteria is met: Body weight ≤ 60 kg, CCr < 50 mL/min, use of P-glycoprotein inhibitor OR Edoxaban 60 mg QD if none of the dosage reduction criteria are met	Less than 30 mg QD if any of the following criteria is met: Body weight ≤ 60 kg, CCr < 50 mL/min, use of P-glycoprotein inhibitor OR Less than 60 mg QD if no dosage reduction criteria are met	More than 30 mg QD if any of the following criteria is met: Body weight ≤ 60 kg, CCr < 50 mL/min, use of P-glycoprotein inhibitor OR More than 60 mg QD if no dosage reduction criteria are met

BID, Twice Daily; CCr, Creatinine Clearance Rate; NOAC, Non-Vitamin K Antagonist Oral Anticoagulant; QD, Once Daily.

Table 2. Demographic and Clinical Characteristics of the Study Groups

		Groups			P
		Off-label Low (n = 140)	On-label (n = 721)	Off-label High (n = 42)	
Age (years)		74.2 ± 9.6	68.1 ± 9.8	73.4 ± 12.1	<0.001
Sex	Female	63 (45.0)	383 (53.1)	29 (69.0)	0.019
	Male	77 (55.0)	338 (46.9)	13 (31.0)	
BMI (kg/m ²)		28.9 ± 5.0	29.7 ± 5.7	25.9 ± 6.1	<0.001
Educational Status	Illiterate	38 (27.1)	167 (23.2)	14 (33.3)	0.358
	Primary School	77 (55.0)	387 (53.7)	24 (57.1)	
	Middle School	11 (7.9)	69 (9.6)	2 (4.8)	
	High School	6 (4.3)	69 (9.6)	1 (2.4)	
	University	8 (5.7)	28 (3.9)	1 (2.4)	
	Post-University (Master's–Doctorate)	0 (0.0)	1 (0.1)	0 (0.0)	
Perception of Income Level	Average: My income covers my expenses.	94 (67.1)	496 (68.8)	26 (61.9)	0.010
	Below Average: I struggle to meet my essential needs.	34 (24.3)	190 (26.4)	15 (35.7)	
	Above Average: I can save money beyond meeting my needs.	11 (7.9)	16 (2.2)	1 (2.4)	
	Poor: I cannot meet my needs at all.	1 (0.7)	19 (2.6)	0 (0.0)	
Drug Discontinuation	Continued	106 (93.0)	576 (91.1)	30 (90.9)	0.807
	Discontinued	8 (7.0)	56 (8.9)	3 (9.1)	
HAS-BLED Score		1.94 ± 1.1	1.5 ± 1.08	2.0 ± 1.1	<0.001
CHA ₂ DS ₂ -VASc Score		3.471 ± 1.42	2.9 ± 1.5	3.3 ± 1.2	<0.001

BMI, Body Mass Index; CHA₂DS₂-VASc, congestive heart failure, hypertension, age ≥ 75 (doubled), diabetes, stroke (doubled), vascular disease, age 65 to 74, and sex category (female); HAS-BLED, Hypertension, Abnormal liver/renal function, Stroke history, Bleeding history or predisposition, Labile INR (International Normalized Ratio), Elderly, Drug/alcohol usage.

Table 3. Dosing Patterns of NOACs in the Study Groups

NOAC	Prescription Patterns n (%)			
	Off-label Low	On-Label	Off-label High	Total
Apixaban	68 (17.5)	309 (79.6)	11 (2.8)	388 (100)
Edoxaban	15 (9)	138 (82.6)	14 (8.4)	167 (100)
Rivaroxaban	57 (16.4)	274 (78.7)	17 (4.9)	348 (100)
Total	140 (15.5)	721 (79.8)	42 (4.7)	903 (100)

NOAC, Non-Vitamin K Antagonist Oral Anticoagulant.

than those in the OFLD and OFHD groups (both $P < 0.001$). Additionally, for the CHA₂DS₂-VASc score, there was a significant difference in the scores between the OL and OFLD groups ($P < 0.001$). Furthermore, the scores in patients in the OL group were significantly lower than those in the OFLD groups (2.939 ± 1.47 vs. 3.471 ± 1.42). However, the other comparisons between the HAS-BLED and CHA₂DS₂-VASc scores were insignificant ($P > 0.05$). There is no significant difference in NOAC preferences in patients for whom a standard dose is indicated ($P = 0.08$). Also, there is no significant difference in terms of NOAC preferences in patients for whom low doses are indicated ($P = 0.50$). The dosing patterns of NOACs in the study groups are shown in Table 3. The majority of patients (79.8%) received the OL doses of NOACs,

while 15.5% and 4.7% received OFLD and OFHD, respectively. There were no significant differences between NOACs in terms of OL, OFLD, or OFHD prescription rates.

Furthermore, there were no statistically significant differences between the groups in terms of laboratory findings, except for hemoglobin, alanine transaminase, creatinine levels, and glomerular filtration rate (GFR). Patients in the OL group had significantly higher hemoglobin levels than those in the OFLD and OFHD groups ($P = 0.016$ and $P = 0.007$, respectively). Additionally, the mean GFR was significantly higher in the OL group than in the other groups (both $P < 0.001$), and significantly higher GFR scores were detected in the OFLD group than in the

Table 4. Laboratory Findings

	Groups			P
	Off-label Low (n = 140)	On-label (n = 721)	Off-label High (n = 42)	
Hemoglobin (g/dL)	12.714 ± 1.79	13.182 ± 1.71	12.296 ± 1.89	<0.001
ALT (IU/L)	20.938 ± 21.19	21.357 ± 14.95	18.785 ± 14.98	0.002
Albumin (g/dL)	4.003 ± 0.71	4.082 ± 0.42	3.815 ± 0.60	0.033
Creatinine (mg/dL)	0.999 ± 0.31	0.92 ± 0.28	1.092 ± 0.41	0.001
GFR	74.105 ± 29.75	88.724 ± 35.19	60.089 ± 41.54	<0.001

ALT, Alanine Transaminase; GFR, Glomerular Filtration Rate.

Table 5. Association Between the Knowledge Levels of Non-Valvular Atrial Fibrillation and NOACs and Dosing Patterns

	Off-label Low (n = 132)	On-label (n = 692)	Off-label High (n = 39)	P
AF Knowledge	48.8 ± 23.0	49.3 ± 23.3	45.1 ± 24.6	0.506
NOAC Knowledge	74.7 ± 20.3	73 ± 19.4	72.2 ± 20.5	0.520

AF, Atrial Fibrillation; NOAC, Non-Vitamin K Antagonist Oral Anticoagulant.

OFHD group ($P < 0.001$). Statistically significant laboratory results are shown in Table 4, while AF and NOAC knowledge levels and dosing patterns are shown in Table 5.

Discussion

In this study, we evaluated the label adherence of NOAC dosing patterns across three NOACs, as well as the association between inappropriate NOAC dosing in patients with NVAF in routine clinical practice. We found that the OL was administered to 79.8% of patients, while 15.5% of patients were prescribed inappropriately low doses of NOACs. Additionally, we observed OFHD (4.7%) prescribed to the study groups; however, it was not possible to evaluate the long-term side effects.

It has been shown that the risk of thromboembolic and hemorrhagic complications in patients who are indicated for low-dose NOACs (apixaban less than 10 mg daily; rivaroxaban less than 20 mg daily; edoxaban less than 60 mg daily) is higher than that in patients suitable for standard doses (apixaban 10 mg daily; rivaroxaban 20 mg daily; edoxaban 60 mg daily).¹¹ However, when low-dose NOACs are prescribed in accordance with the approved indications, recommendations, and product information, no difference is observed in terms of safety compared to standard-dose NOACs.²⁵ Our evaluation of compliance with approved dosing showed slightly lower adherence rates compared to those reported in the literature^{8,21-23}

Since routine monitoring of drug concentrations is not necessary for NOACs, it is crucial to select the correct dose based on approved dosing guidelines. However, off-label NOAC dosing remains an issue in everyday clinical practice. A prior report from the United States indicated that about 9.4% of patients with NVAF were given OFLD NOACs, leading to poor clinical outcomes.⁸ Given the higher bleeding risk, such as intracranial hemorrhage, in the Asian population, physicians often prescribe low-dose NOACs for Asian patients with AF in daily practice.⁹ In fact, in Taiwan, the on-label doses of rivaroxaban (20 mg/day), dabigatran (150 mg

twice daily), and apixaban (5 mg twice daily) are prescribed to only 12%, 6%, and 38% of NVAF patients, respectively.¹⁰ In our study, the rate of OFLD NOAC prescriptions was similar to that reported in previously published studies.²⁵

The prescribed dose of NOACs should take into account the patient's body weight, age, renal function, other medications, and conditions that increase bleeding risk. Consequently, a complete blood count, along with renal and liver function tests and a coagulation panel, should be obtained from patients before starting NOAC therapy.^{16-18,26}

The current study revealed that the patients who received OFLD or OFHD were older than those who were prescribed OL. Although there are different dose-reduction criteria for different NOACs, it may be possible for patients to encounter not only age-related dose-reduction criteria as they age but also worsening laboratory results and the use of multiple drugs. Such cases may require physicians to apply the dose-reduction criteria.²⁷

In addition, weight should be evaluated according to the dose-reduction criteria for apixaban and edoxaban. In this study, the significant differences between the BMI values of patients might have affected the comparison of our results with those of other studies.^{16-18,26}

In our study, the HAS-BLED scores in the OL group were significantly lower than those in the OFLD group. Notably, in the HAS-BLED scoring system, criteria other than age, body weight, and kidney function are not included in the NOAC dose-reduction criteria. This may explain why some physicians take the initiative and prefer prescribing low doses in the group with high HAS-BLED scores. Sato et al.²⁸ showed that the HAS-BLED scoring system, which is a practical tool for assessing the risk of MB in patients with AF, can independently predict the underdosing of apixaban (odds ratio [OR], 1.59; 95% confidence interval [CI], 1.18-2.13) and rivaroxaban (OR, 2.27; 95% CI, 1.51-3.39). This aligns with our finding that inappropriate NOAC dosing is

significantly associated with higher HAS-BLED scores. This also applies to the CHA2DS2-VASc scoring system. In this scoring system, criteria other than age may not be used directly as dose-reduction criteria. This may cause physicians to disregard their prescribing habits based on indications, which is consistent with our results. Notably, hemoglobin levels could be useful to evaluate the severity of bleeding and to determine the necessity of red blood cell transfusion.²⁹ In the current study, hemoglobin levels were significantly lower in the OFLD and OFHD groups. However, we could not evaluate the reasons for the significantly lower hemoglobin levels in patients with inappropriate NOAC use. Therefore, prospective studies are required to clarify the possible association between NOAC use and the development of anemia.

Different NOACs have different GFR limits and creatinine clearance values for dosing. Therefore, creatinine clearance and levels should be measured in patients with significant bleeding.²⁹ In addition to the significant differences in creatinine levels between the groups, the GFR values were lower in the OFHD group than in the other study groups. We believe that there may be no direct relationship between renal function and the prescription of OFHD NOACs. Furthermore, in this study, the number of patients prescribed OFHD NOACs was lower than that in the OL and OFLD groups. Moreover, the mean GFR was significantly higher in the OL group than in the other groups (both $P < 0.001$). This result can indicate the lack of knowledge or confusion of the dose-reduction criteria among physicians. It is known that different NOACs require dose reductions at different GFR levels.³⁰ This can be particularly challenging for physicians who do not adhere to a single NOAC regimen.

The number of female patients was significantly higher in the OFHD group, whereas that of male patients was significantly higher in the OFLD group. Similar to our study, there are studies that show that OFHD is common in female patients^{31–34} However, the differences in sex distribution between the groups may resemble the overall disease groups instead of indicating different trends in NOAC use.

Off-label NOAC prescription was common among patients with NVAF who required standard dosing according to the guidelines, but lower than in previous studies that reported high rates of underdosing of NOACs.^{36,37} This may reflect an improvement in physicians' awareness of the appropriate dosing criteria and the guidelines' recommendations to monitor the clinical and laboratory parameters of patients under NOAC treatment regularly.

In our study, we did not find any significant differences between the knowledge levels of NVAF and NOACs and dosing patterns. While the off-label dosing decision is made here, physicians may not make off-label decisions due to insufficient NVAF and NOAC information levels. In making this decision, a physician's own clinical experience may play a more prominent role.

Our study had some limitations. First, because this study was primarily observational with descriptive results, it did not monitor the patient awareness of NOAC therapies and knowledge retention for AF over time. Additionally, we did not record the concurrent use of nonsteroidal anti-inflammatory drugs and antiplatelet medications, which may be significant factors in the intentional undertreatment with NOACs. Due to the nature

of observational studies, we could not establish a cause-and-effect relationship; thus, we cannot fully explain why physicians prescribed NOACs off-label. Furthermore, detailed explanations for the termination of NOAC were not actively sought. This study focused on a specific population at a single time point, which may not capture changes over time and also limits the generalizability of the findings. Consequently, our findings should be evaluated cautiously and used to inform the development of hypotheses for future research.

Conclusion

In conclusion, OFLD NOAC prescription was common among the Turkish population who required standard dosing; however, this was also lower than in previous reports.^{35,37} There are different dosing criteria for different NOACs; therefore, this may lead to inappropriate dosing in busy outpatient settings, as we observed in Türkiye. This situation may be even more challenging for physicians who prefer prescribing different NOACs in their daily practice. The clinical impact of low-dose NOAC prescriptions may vary considerably depending on the type of NOAC prescribed. Raising clinician awareness about proper NOAC dosing could aid in identifying patients who are at risk. Therefore, prospective studies should be performed to evaluate the cause-and-effect relationship between NOAC use and systemic complications such as anemia and renal dysfunction.

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Informed Consent: All patients were informed about the study and provided written informed consent before participating in any study-related activities.

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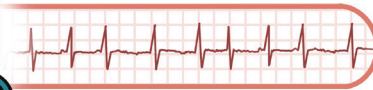
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Assessment of Non-Vitamin K Antagonist Oral Anticoagulant (NOAC) Dosing Patterns in Turkish Patients with Non-Valvular Atrial Fibrillation:

A Multicenter, Cross-Sectional Study with Insights from the ASPECT-NOAC Study

- Observational
- Prospective
- Cross-sectional
- Multicenter study



903 pts w/ AF who were prescribed NOAC



34 cardiology centers in Türkiye



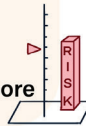
Age (years)



BMI (kg/m²)

HAS-BLED Score

CHA2DS2-VASc Score



Off-label Low (n = 140)

On-label (n = 721)

Off-label High (n = 42)

74.2 ± 9.6 68.1 ± 9.8 73.4 ± 12.1 p<0.001

28.9 ± 5.0 29.7 ± 5.7 25.9 ± 6.1 p<0.001

1.94 ± 1.1 1.5 ± 1.08 2.0 ± 1.1 p<0.001

3.471 ± 1.42 2.9 ± 1.5 3.3 ± 1.2 p<0.001



The clinical impact off-label NOAC prescriptions may vary. Therefore, raising clinician awareness about proper NOAC dosing could aid in improve the outcomes.