ORIGINAL RESEARCH

Evaluation of drug adherence in patients with non-valvular atrial fibrillation according to geographic regions of Turkey: An analysis from NOAC-TR study

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Abstract

Drug adherence to novel oral anticoagulants (NOAC) varied by countries and populations. As a result of NOAC-TR study, in Turkey, drug adhrence to NOACs is poor comparing to other real world studies. However it is not known whether there is a difference between geographic regions of Turkey in terms of NOAC adherence. In this study we aim to investigate the NOAC adherence in patients with non-valvular atrial fibrillation according to the geographic regions in Turkey Method: This cros-sectional study was designed as a subgroup study of NOAC-TR (Drug Adherence in patients with non valvular atrial fibrillation taking non-vitamin K antagonist oral anticoagulants in Turkey). A total of 2802 patients (59% female) taking NOAC (Dabigatran, apixaban, rivaroxaban) due to NVAF at least 3 months, were included. Morisky-8 item drug adherence scale was used. Patients were divided in 3 groups (high, moderate and low adherent) based on drug adherence Results: Of the patients 24% were adherent, 26% were moderate adhererent and 50% were low adherent to NOAC treatment. Drug adhrence was different between geographic regions (p<0,001). In post-hoc analysis low adherent rate was highest in Blacksea region (72% low adherent, 21% moderate adherent, 7% low adherent). Adherence rate was highest in Aegean (36% adherent, 26% moderate adherent 38%) and Marmara region (38% adherent, 28% moderate adherent 34% low adherent). Conclusion: NOAC adherence was different between geographic regions in Turkey.

Keywords: Novel oral anticoagulants, drug adherence, morisky scale, geographic differences

Introduction

Atrial fibrillation (AF) is one of the most frequently encountered causes of cardiovascular mortality and morbidity [1]. Vitamin K antagonists (VKAs) are the oldest and most widely used anticoagulant drugs in the treatment of AF. Although VKAs are efficient medications in the treatment and prevention of thromboembolic diseases, they have important disadvantages such as narrow therapeutic range, delayed onset and offset of action, and potential of interaction with diet and other drugs [2].

Such disadvantages therefore necessitate close monitoring and follow-up in order to maintain patients receiving VKAs within a therapeutic anticoagulant range (time in therapeutic range, TTR). New oral anticoagulant medications have been developed to eliminate disadvantages of VKAs and their efficiency and safety profiles have been validated in randomized and controlled studies [3-8].

Rapid onset of action, fixed-dose combination, and lack of need for monitorization are the main advantages of NOACs over VKAs [9,10]. These characteristics reduce the frequency of outpatient visits. However, skipping a single dose rapidly decreases the efficiency of NOACs as these drugs have short half-life [3]. This feature attributes particular importance on adherence of NOAC therapy. There is a paucity of real world data regarding adherence to NOAC therapy and the level of drug adherence varies between different populations. The rate of adherence of NOAC therapy was reported to be 49% in NOAC-TR study [11]. However, there is no data on to what extent geographic regions differ from each other in terms of adherence to NOAC therapy.

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The present study evaluated whether adherence to NOAC therapy in patients with non-valvular AF (NVAF) differs between geographic regions of Turkey.

Material and Methods

The present study was conducted as a subgroup analysis of the NOAC-TR study (Evaluation of drug adherence in patients receiving therapy with new oral anticoagulant drugs. This multicenter, cross-sectional study was conducted between September 2015 and February 2016 in 45 centers, covering 7 different geographic regions of Turkey. The study population was composed of patients who previously received VKAs, as the Ministry of Health and Social Security Institution of Turkey have postulated that patients must have failed to achieve sufficient TTR or have sustained ischemic stroke under VKAs therapy for the reimbursement of NOAC therapy. In total, 2802 patients aged 18 years or older who were followed by the cardiology and cardiovascular outpatient clinics and who received therapy with dabigatran (110-150 mg), rivaroxaban (20-15 mg) or apixaban (5-2.5 mg) in the last 3 months due to NVAF. Of these patients, 975 were from the Central Anatolia Region, 577 were from the Aegean Region, 409 were from the Marmara Region, 391 were from the Black Sea Region, 184 were from the Mediterranean Region, 158 were from the Eastern Anatolia Region, and 105 were from the Southeastern Anatolia Region.

The study was approved by Afyonkarahisar Clinical Research Ethics Committee (Decision no: 2015/12-334). All patients provided written informed consent to participate in the study. Patients with an insufficient sociocultural status to complete the questionnaire and patients who received NOAC therapy for less than 3 months were excluded. All patients completed the questionnaire. The questionnaire contained questions about demographic data, NOAC therapy received, past medications and previous diseases. The CHA2DS2-VASc (congestive heart failure/left ventricular dysfunction, hypertension, age ≥ 75 (2 points), diabetes, stroke (2 points) – vascular disease, 65-74 age range and female gender) and HAS-BLED scores (Hypertension, abnormal liver/kidney function, stroke history, prior major bleeding or predisposition to bleeding, labile INR, age (age$\geq$65, fragility), alcohol/drug usage history) were calculated for each patient. The questions of 8-item Morisky Medication Adherence Scale were included in the final section to evaluate adherence to NOAC therapy.

Morisky Medication Adherence Scale

The Morisky Medication Adherence Scale has been previously validated in the evaluation of drug adherence in patients on VKAs [12]. Instead of using the original 4-item Morisky Scale, 8-item version of the scale was used to better determine the conditions and circumstances that could affect drug adherence and better evaluate psychometric characteristics (Table 1) [13]. The validity and reliability of the Turkish version of the 8-item Morisky Medication Adherence Scale was previously evaluated for use in the Turkish population [14,15].

Table 1. Eight-item Morisky Medication Adherence Scale

Questions	Patient's Response (Yes/No)
1. Do you sometimes forget to take your medications?	Yes: 1 point No: 0 points
2. People sometimes miss taking their medications for reasons other than forgetting. Thinking over the past two weeks, were there any days when you did not take your medicines?	Yes: 1 point No: 0 points
3. Have you ever cut back or stopped taking your medication without telling your doctor, because you felt worse when you took it?	Yes: 1 point No: 0 points
4. When you travel or leave home, do you sometimes forget to bring along your medications?	Yes: 1 point No: 0 points
5. Did you take your medications yesterday?	Yes: 0 point No: 1 points
6. When you feel like your condition is under control, do you sometimes stop taking your medicines?	Yes: 1 point No: 0 point
7. Taking medication everyday is a real inconvenience for some people. Do you ever feel hassled about sticking to your treatment plan?	Yes: 1 point No: 0 points
8. How often do you have difficulty remembering to take all your medications?	A: 0 points
A: Never/Rarely, B: Occasionally, C: Sometimes, D: Often, E: Always	B-E: 1 point

Total Score: >2 = non-adherent   1 or 2 = moderately adherent   0 = adherent

In this scale, each question is scored as 1 or 0 depending on Yes and No responses and sum of all scores yields the final score. Accordingly, the highest score would be 8 points and the lowest score would be 0 point. In classical 8-item Morisky Medication Adherence scale, a score of 8 points indicate good adherence, a score of 6-8 points indicate moderate adherence, and a score of 5 points or lower indicate non-adherence.

Statistical Analysis

The statistical analysis was performed using SPSS for Windows 15.0 (SPSS Inc., Chicago, IL, USA) software package. The numerical data were expressed as mean and standard deviation, and categorical data were expressed as frequency and ratio. One-way ANOVA was used for numerical data to compare the variables between geographic regions. The least significance difference (LSD) test was

used in the comparison of subgroups. Chi-square test was used to compare proportional data. In all analyzes, the level of statistical significance (Type I error) was set at p < 0.05.

Results

The mean age of the patients was 70.±10.6 years. The mean age was the lowest in the Central Anatolia Region (67.2±11.3 years) and highest in the Black Sea Region (75±8.4 years). Of the study population, 59% were females. The female-to-male ratio was high in all regions. The ratio of female patients was the highest in the Eastern Anatolia Region (65%) and lowest in the Aegean Region (56%). The duration of therapy with NOACs was the shortest in the Eastern Anatolia Region (318±242 days) and the longest in the Aegean region (409±285 days).

The study patients were composed of those who previously received VKAs and switched to therapy with NOACs afterwards. Rivoraxaban was the most commonly used NOAC in the Central Anatolia and Marmara Regions and dabigatran was the most commonly used NOAC in the other regions.

In terms of educational status, illiterate patients comprised the majority of the patients in the Eastern and Southeastern Anatolia Regions, whereas primary school graduates were the largest group in the other regions. Apart from these differences, all geographic regions were comparable in terms of occupations of the patients, place of living, rates of patients living alone, concurrent use of medications, drug and alcohol dependence, knowledge of medication and disease, drug self-administration, forgetfulness , and side effects (Table 2).

Table 2. Comparison of demographic characteristics of the patients between geographic regions

	Central Anatolia	Aegean	Marmara	Black Sea	Mediterranean	Eastern Anatolia	Souteastern Anatolia	P
Age, year (mean ± S.D.)	67.2±11.3	71.8±9.4	72.2±9.8	75±8.4	70±10.9	69.1±10.2	71.8±9.8	<0.001
Gender, female n (%)	599 (61%)	321 (56%)	232 (57%)	235 (60%)	111 (60%)	103 (65%)	60 (57%)	0.195
Duration of NOAC use, days (mean ± S.D.)	345±193	409±285	377±236	333±222	334±184	318±242	370±262	<0.001
NOAC received								
Dabigatran, n (%)	339 (35%)	293 (51%)	152 (37%)	242 (62%)	85 (46%)	70 (44%)	54 (52%)	
Rivaroxaban, n (%)	394 (40%)	210 (36%)	176 (43%)	127 (32%)	59 (32%)	64 (41%)	45 (43%)	<0.001
Apixaban, n (%)	242 (25%)	73 (13%)	80 (20%)	22 (6%)	40 (22%)	24 (15%)	5 (5%)	
Use of double doses per day, n (%)	581 (59%)	366 (63%)	232 (57%)	264 (67%)	125 (68%)	94 (59%)	59 (56%)	0.011
Level of education								
Illitirate, n (%)	269 (28%)	156 (27%)	141 (34%)	134 (34%)	50 (27%)	75 (47%)	80 (76%)	
Primary school, n (%)	423 (43%)	299 (52%)	213 (52%)	205 (52%)	80 (44%)	47 (30%)	19 (18%)	
Secondary school, n (%)	124 (13%)	49 (9%)	19 (5%)	40 (10%)	26 (14%)	19 (12%)	3 (3%)	<0.001
High-school, n (%)	128 (13%)	36 (6%)	28 (7%)	11 (3%)	24 (13%)	14 (9%)	3 (3%)	
University, n (%)	34 (3%)	36 (6%)	8 (2%)	1 (0.3%)	4 (2%)	3 (2%)	0 (0%)	
Employment Status								
Unemployed, n (%)	570 (58%)	227 (42%)	184 (46%)	252 (65%)	87 (49%)	71 (56%)	93 (89%)	
Employed, n (%)	290 (30%)	298 (55%)	209 (52%)	131 (33%)	86 (49%)	54 (42%)	9 (9%)	<0.001
Retired, n (%)	116 (12%)	14 (3%)	10 (2%)	8 (2%)	4 (2%)	3 (2%)	3 (2%)	
Place of living								
City center, n (%)	297 (30%)	227 (42%)	112 (27%)	114 (29%)	37 (21%)	37 (29%)	41 (39%)	
District, n (%)	380 (39%)	183 (34%)	257 (63%)	172 (44%)	80 (45%)	83 (65%)	40 (38%)	<0.001
Village, n (%)	301 (31%)	131 (24%)	40 (10%)	105 (27%)	61 (34%)	8 (6%)	24 (23%)	
Living alone, n (%)	126 (13%)	66 (12%)	52 (13%)	15 (4%)	13 (7%)	5 (3%)	15 (14%)	
Number of concurrent medications, n (%)								
0	1 (0.1%)	19 (3%)	1 (0.2%)	0 (0%)	1 (0.5%)	0 (0%)	1 (1%)	
0-4	375 (38%)	309 (54%)	165 (44%)	182 (46%)	97 (53%)	78 (49%)	39 (38%)	<0.001
5 and higher	602 (62%)	48 (43%)	243 (55%)	209 (54%)	86 (46%)	80 (51%)	63 (62%)	
Drug dependence, n (%)	11 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0.002
Alcohol dependence, n (%)	21 (2%)	23 (4%)	0 (0%)	1 (0.3%)	3 (2%)	0 (0%)	0 (0%)	<0.001
Knowledge about the drug and disease, n (%)	698 (71%)	417 (72%)	250 (61%)	251 (64%)	143 (78%)	106 (67%)	22 (21%)	<0.001
Self-administration of the drug, n (%)	716 (73%)	452 (78%)	270 (66%)	290 (74%)	127 (69%)	143 (90%)	60 (57%)	<0.001
Forgetfulness, n (%)	324 (33%)	219 (38%)	194 (47%)	151 (39%)	64 (35%)	7 (4%)	71 (68%)	<0.001
Side effects, n (%)	65 (7%)	103 (18%)	34 (8%)	47 (12%)	26 (14%)	1 (1%)	10 (9%)	<0.001

NOAC: New Oral Anti-Coagulant, n: number; S.D.= standard deviation

The mean CHA2DS2-VASc score was different across geographic regions (p<0.001) (Table 3). Post hoc analysis did not reveal a significant difference between the mean CHA2DS2-VASc scores in Southeastern Anatolia, Mediterranean, Black Sea, and Marmara Regions, whereas the mean CHA2DS2-VASc score found to be lower in the Eastern Anatolia Region when compared with the other geographic regions (Table 4). The mean HAS-BLED score was also different across geographic regions (p<0.05) (Table 5). In post hoc analysis, the mean HAS-BLED score was higher in the Southeastern Anatolia Region compared with the other regions, whereas comparison between the all

other geographic regions revealed no significant difference (Table 6). Among comorbid conditions, the rates of pulmonary embolism and deep venous thrombosis were comparable between geographic

regions (p>0.05), whereas other clinical risk factors showed significant difference between the regions (p<0.05).

In the whole study group, 24% of the patients were adherent, 26% were moderately adherent, and 50% were non-adherent. The level of adherence to drug therapy varied significantly between geographic regions (p<0.001). The rate of non-adherent patients was the highest in the Black Sea Region (72%), and it was followed by the Southeastern Anatolia Region (65%), Mediterranean Region (63%), Central Anatolia Region (52%), Eastern Anatolia Region (46%), Aegean Region (38%), and Marmara Region (34%) (Figure 1). In paired comparisons, the rate of drug-adherent patients was different from all other regions, whereas there was no difference between Southeastern and Mediterranean Regions, and between Aegean and Marmara Regions (Table 6).

Table 3. Distribution of demographic characteristics of the patients according to geographic regions

|	Central Anatolia	Aegean	Marmara	Black Sea	Mediterranean	Eastern Anatolia	Souteastern Anatolia	P
CHA2DS2-VASc score, mean±S.D.	3.4±1.3	3.3±1.5	3.6±1.5	3.6±1.4	3.6±1.5	3.1±1.2	3.9±1.4	<0.001
HAS-BLED score, mean±S.D.	2.2±1.1	2.2±1.2	2.1±0.9	2.1±0.8	2.3±0.8	2.2±0.8	2.6±1	0.020
Pulmonary embolism, n (%)	28 (3%)	9 (2%)	13 (3%)	7 (2%)	8 (4%)	1 (1%)	2 (2%)	0.152
Deep venous thrombosis, n (%)	48 (5%)	11 (2%)	18 (4%)	13 (3%)	8 (4%)	6 (4%)	1 (1%)	0.058
Hypertension, n (%)	752 (77%)	450 (78%)	317 (77%)	314 (80%)	151 (82%)	118 (75%)	98 (93%)	0.004
Diabetes mellitus, n (%)	295 (30%)	160 (28%)	92 (22%)	43 (11%)	41 (22%)	39 (25%)	16 (15%)	<0.001
Smoking, n (%)	150 (15%)	103 (18%)	19 (5%)	50 (13%)	35 (19%)	78 (49%)	14 (13%)	<0.001
Hyperlipidemia, n (%)	317 (32%)	151 (26%)	96 (23%)	123 (31%)	49 (27%)	44 (28%)	16 (15%)	<0.001
Heart failure, n (%)	183 (19%)	161 (28%)	103 (25%)	107 (24%)	55 (30%)	69 (44%)	34 (32%)	<0.001
Coronary artery disease, n (%)	294 (30%)	140 (24%)	97 (24%)	43 (11%)	51 (28%)	102 (65%)	41 (39%)	<0.001
Stroke, n (%)	91 (9%)	53 (9%)	62 (15%)	66 (17%)	32 (17%)	18 (11%)	21 (20%)	<0.001
Peripheral arterial disease, n (%)	43 (4%)	6 (1%)	5 (1%)	13 (3%)	15 (8%)	0 (0%)	3 (3%)	<0.001
Chronic kidney failure, n (%)	90 (9%)	45 (8%)	39 (9%)	9 (2%)	11 (6%)	3 (2%)	3 (3%)	<0.001
Depression, n (%)	130 (13%)	72 (12%)	36 (9%)	39 (10%)	24 (13%)	3 (2%)	7 (7%)	<0.001
Dementia, n (%)	86 (9%)	61 (11%)	38 (9%)	88 (22%)	45 (24%)	2 (1%)	8 (8%)	<0.001
Other psychotic diseases, n (%)	43 (4%)	30 (5%)	10 (2%)	38 (10%)	19 (10%)	0 (0%)	7 (7%)	<0.001

n: number

Table 4. Post-hoc analysis of drug adherence according to geographic regions

	Aegean	Eastern Anatolia	Central Anatolia	Mediterranean	Southeastern Anatolia	Black Sea
Marmara	0.428	0.046	<0.001	<0.001	<0.001	<0.001
Aegean		0.248	<0.001	<0.001	<0.001	<0.001
Eastern Anatolia			0.002	<0.001	<0.004	<0.001
Central Anatolia				0.030	0.041	<0.001
Mediterranean					0.797	0.007
Southeastern Anatolia						0.019

Table 5. Post-hoc analysis of CHA2DS2-VASc score according to geographic regions

	Aegean	Eastern Anatolia	Central Anatolia	Mediterranean	Southeastern Anatolia	Black Sea
Marmara	0.002	<0.001	0.008	0.757	0.096	0.888
Aegean		0.037	0.371	0.036	<0.001	0.003
Eastern Anatolia			0.006	0.001	<0.001	<0.001
Central Anatolia				0.105	0.001	0.014
Mediterranean					0.086	0.845
Southeastern Anatolia						0.080
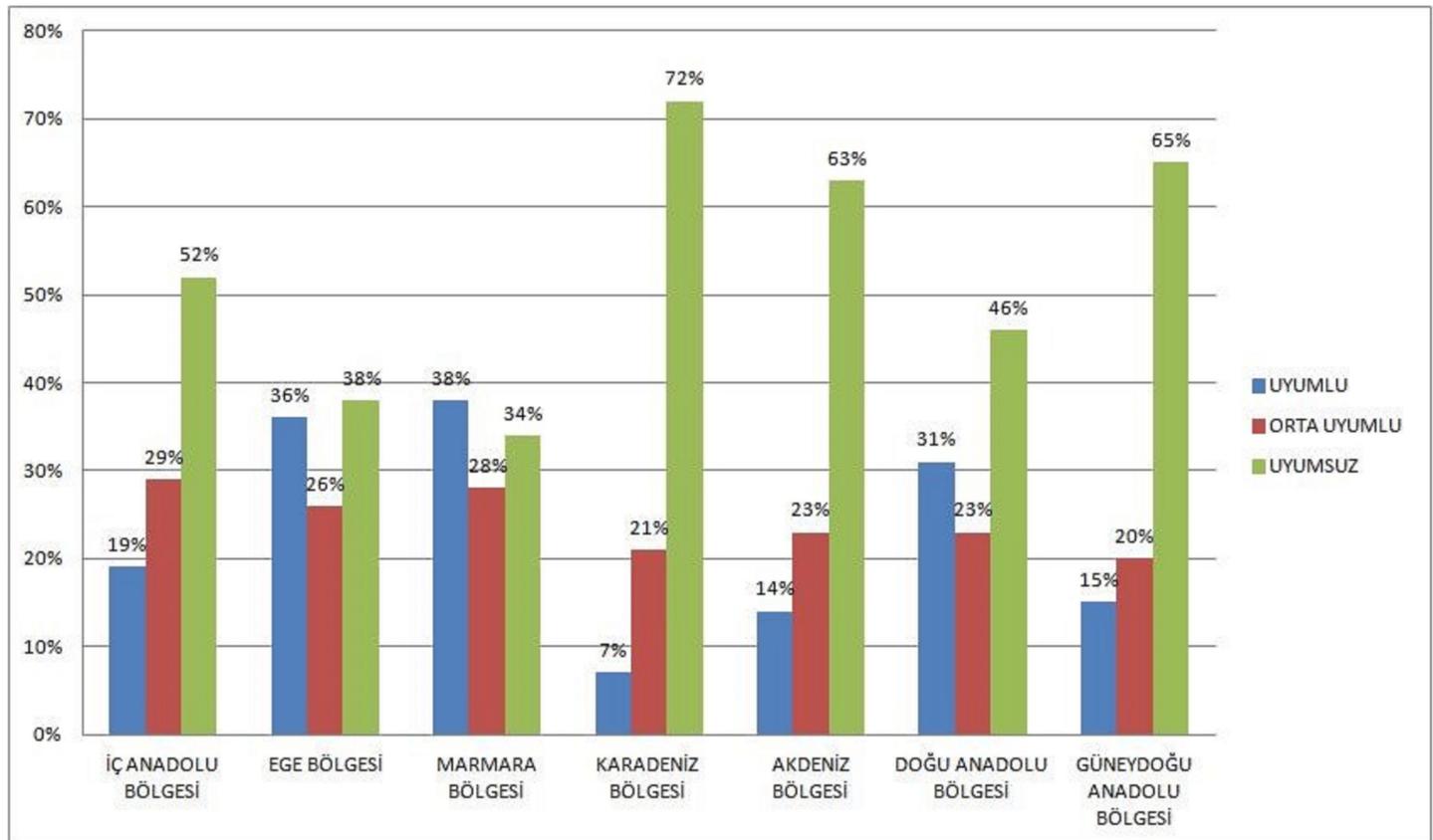
Figure 1. Evaluation of adherence to NOAC therapy according to geographic regions

Discussion

To our knowledge, the present multicenter study is the first to evaluate adherence to therapy with NOACs in according to geographic regions of Turkey in patients with NVAF.

High drug adherence is of vital importance for an efficient and successful anticoagulant therapy. There is a direct relationship between decrease in adherence to NOAC therapy and increase in cardioembolic events [16, 17]. Phase 3 studies have often reported a rate of drug adherence higher than 90% in patients receiving NOAC therapy [4, 5, 6, 18]. Higher rates of drug adherence in phase 3 studies are considered to be associated with selection of patients having lower potential for non-adherence, motivation of the patients strictly by the investigators for drug administration, and frequent clinic visits during the course of the study. It is a striking finding that data from randomized studies do not align with the real-world data. The studies reflecting the real-world data report

a wide range of drug adherence from 47.7% to 95% [19-22]. The real-world studies have reported different rates of drug adherence due to differences in the study population and study samples, duration of follow-up, different indications for the use of NOAC therapy, and differences in methods to evaluate drug adherence. The present study was conducted on a large population, which was composed of patients who received NOAC therapy for a prolonged period due to NVAF. The overall rate of drug adherence was found to be 50% using 8-item Morisky Medication Adherence Scale. The Black Sea, Mediterranean, Southeastern, and Central Anatolia Regions had lower rates of drug adherence when compared to average rates for Turkey. The rates of drug adherence in Marmara and Aegean Regions were above the average rates for Turkey.

Causes of Non-adherence

There is no sufficient data regarding the factor affecting drug adherence in patients receiving NOAC therapy. The available data derive from the experiences on patients using VKAs. Various

studies have shown that adherence to therapy with VKAs were affected by ethnical origin, economic status, educational level, employment status, missing doses, lack of knowledge on drug usage, use of additional drugs, drug and alcohol dependence, and emotional factors [23-26]. IN-RANGE study investigated factors affecting adherence to therapy with VKAs for the duration of 32 months. Smoking status, employment status, drug usage indications, impaired quality of life, and presence of cognitive impairment were reported as factors affecting drug adherence [27]. In the NOAC-TR study, depression, dementia, age, administration of drug by another person, side effects, administration of 5 or more drugs, living in a village, use of double doses per day, educational level, and drug knowledge were identified as independent risk factors affecting drug adherence [11]. In the present subgroup analysis, each of the risk factors affecting drug adherence were different between geographic regions. For instance, age, use of double doses per day, low educational level (illiterate and primary school graduate), and dementia were the most prominent risk factor in the Black Sea Region that showed the lowest rate of adherence to NOAC therapy. Low educational level, unemployment, use of 5 or more drugs, lack on knowledge on the drug and disease, administration of the drug by another person, and missing doses were predominating risk factors in the Southeastern Anatolia region, which ranked second in terms of non-adherence to drug therapy. The use of double doses per day, living in a village, depression, and dementia were prominent risk factors in the Mediterranean Region, which ranked third among other geographic regions in terms of non-adherence to drug therapy.

As per the conditions postulated by the Social Security Institution in Turkey, almost all patients receiving NOAC therapy due to NVAF are composed of patients who have previously received therapy with VKAs. The TTR is low in the majority of these patients. In a nation-wide Warfain-TR study, the mean TTR was reported to be 49.5± 22.9% among patients receiving VKAs [28]. In a subgroup analysis, the mean TTR was found to be the highest in the Marmara Region and lowest in the Southeastern Region. Age, female gender, drug knowledge, renal failure, HAS-BLED score, and CHA2DS2-VASc score were identified as independent factors affecting TTR [29]. In the present study, variability in drug adherence between geographic regions was found to be similar to the variability in TTR values. Although the present study did not evaluate TTR values, it is considered based on the current data that previous TTR values of the patients might have affected drug adherence. Based on the conditions of Turkey, before switching VKA to NOAC, one should consider to previous TTR and the factors affecting TTR while using VKA.

Study Limitations
The data obtained from this study are based on hospital records and patient-reported data that may have biased the study results. Test methods used to evaluate drug adherence have individual advantages and disadvantages. Although there is no gold standard method, drug adherence might have been overestimated or underestimated as Morisky Medication Adherence Scale relies on the responses provided by the patients.

Furthermore, selection of all study patients from those who have failed to achieve sufficient TTR under VKA therapy or who have sustained cardioembolic events might have caused underestimation of drug adherence level.

Conclusion

The adherence to therapy with NOACs as measured by 8-item Morisky Medication Adherence scale in patients with NVAF varies between geographic regions. The difference in drug adherence between geographic regions derives from the differences in demographic characteristics and clinical factors.

Acknowledgements

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