New oral anticoagulants-TURKey (NOAC-TURK): Multicenter cross-sectional study

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ABSTRACT

Objective: New oral anticoagulants (NOACs) are increasingly used both for prevention of stroke in non-valvular atrial fibrillation (NVAF) and the treatment of venous thromboembolism (VTE). In this study, we aimed to evaluate the current patterns of NOACs treatment in Turkey. Moreover, demographic and clinical parameters and bleeding and/or embolic events under NOACs treatment were analyzed.

Methods: The New Oral Anticoagulants-TURKey (NOAC-TURK) study was designed as a multicenter cross-sectional study. A total of 2,862 patients from 21 different centers of Turkey under the treatment of NOACs for at least three months were included in this study. Demographic, clinical, and laboratory characteristics of study participants with their medications used were obtained through the NOAC-TURK survey database. Additional necessary medical records were obtained from electronic health records of participating centers.

Results: Of the 2. 862 patients, 1.131 (39.5%) were male and the mean age was 70.3±10.2 years. Hypertension was found as the most frequent comorbidity (81%). The most common indication for NOACs was permanent atrial fibrillation (83.3%). NOACs were mainly preferred because of inadequate therapeutic range or overdose during warfarin usage. The most frequent complication was bleeding (n=217, 7.6%), and major bleeding was observed in 1.1% of the patients. Embolic events were observed in 37 patients (1.3%). Rivaroxaban and dabigatran were both more preferred than apixaban. Almost half of the patients (47.6%) were using lower doses of NOACs, which is definitely much more than expected.

Conclusion: The NOAC-TURK study showed an important overview of the current NOACs treatment regimens in Turkey. Although embolic and bleeding complications were lower than or similar to previous studies, increased utilization of low-dose NOACs in this study should be considered carefully. According to the results of this study, NOACs treatment should be guided through CHA_2DS_2-VASc and HASBLED scores to ensure more benefit and less adverse effects in NVAF patients. *(Anatol J Cardiol 2017; 17: 353-61)*

Keywords: new oral anticoagulants, atrial fibrillation, embolic complication, bleeding

Introduction

Oral anticoagulants (OACs) are the mainstay therapy used for stroke prevention in non-valvular atrial fibrillation (NVAF) and the treatment of venous thromboembolism (VTE). Atrial fibrillation (AF) is the major indication for OACs use and is one of the leading causes of major cardiovascular events, including mortality and fatal stroke worldwide (1). Conventional preventive strategies of AF, such as proper anticoagulant and rate-limiting therapeutic agents, are crucial to avoid its complica-

tions. For over 50 years, vitamin K antagonists such as warfarin, phenprocoumon, and acenocoumarol were the only available oral anticoagulants. Problems like narrow therapeutic window, common food and drug interactions, and the need for repeated blood tests to establish the target international normalized ratio (INR) are the main drawbacks of these drugs during clinical use. These common problems of vitamin K antagonists led to the investigation of more effective and safe anticoagulants. New oral anticoagulants (NOAC) are a result of these studies and have become widely available. Dabigatran (a factor II or thrombin in-

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hibitor), rivaroxaban, and apixaban (factor Xa inhibitors) were approved NOACs in our country. Edoxaban and betrixaban will soon be available worldwide. Dabigatran and rivaroxaban have been approved for non-valvular AF, deep vein thrombosis (DVT), and pulmonary embolism (PE), and apixaban has been approved only for NVAF by the Turkish Ministry of Health. Since their approval, substantial numbers of patients were prescribed NOACs.

The prevalence of AF in Turkey is 1.25% and its incidence is 1.35/1000 person-years according to the Turkish Adult Risk Factor (TARF) study, wherein rheumatic valve disease was regarded as a predisposing factor in only 6.0% of the subjects (2). Reported incidence of VTE along with PE is highly variable because of diagnostic challenges. Estimated annual incidence of VTE ranges from 104 to 183 per 100,000 person-years, and these rates are similar to stroke (1–6). Considering these facts, an increasing number of patients will be prescribed NOACs in our country.

Recently, very important information has been gathered on AF by registries, which include data on large cohorts. These registries were especially important to observe the control of AF and its complications in different patient populations. In the GARFIELD registry, it has been shown that 11.7% of the patients were not using any antithrombotic treatment, whereas 50% were receiving warfarin and 10.8% were using NOACs (7). There are a few recent data sources available in the literature in terms of the efficacy and safety of NOACs, among which only one arose from Turkey (8). However, there is no study that assesses the efficacy and safety of NOACs for all indications, including NVAF, DVT, and PE, in the same study. In this multicenter cross-sectional study, we primarily aimed to assess the current patterns of NOACs treatment to identify therapeutic trends and aspects of the current practice in Turkey. In addition, demographic characteristics, along with bleeding and thromboembolic risk factors of these patients, clinical indications and their conformity to guidelines, adverse effects, and bleeding and embolic complications will be analyzed in this study.

Methods

Study design
The NOAC-TURK study is a national, nonrandomized multicenter cross-sectional study.

Study population
The study was conducted in outpatient cardiology clinics of state, university, private, and training and research hospitals. Included study centers were chosen according to clinical feasibility and also whether or not they represent the Turkish population well. The study centers were initially included in each of the seven geographic regions (Marmara, Aegean, Mediterranean, Central Anatolia, Black Sea, East Anatolia, and Southeast Anatolia), which were composed of 26 different centers in Turkey to provide geographic diversity. However, five centers were excluded from the final data analysis of the study because of non- or low patient (<20 patients/center) recruitment. The study was conducted between August 1, 2015, and January 1, 2016.

In this study, consecutive patients aged ≥18 years with a diagnosis of non-valvular AF, PTE, and/or VTE under the treatment of NOACs for at least three months were included. Patients could be in sinus rhythm or AF at the time of enrollment, but an electrocardiographically confirmed AF episode should have occurred prior to enrollment in NVAF patients. Patients with hypertension; renal failure; coronary artery disease (a history of percutaneous intervention or coronary artery bypass graft surgery); diabetes mellitus; congestive heart failure; and valvular disorders including any degree of mitral regurgitation, aortic stenosis, or aortic regurgitation were included. The exclusion criteria regarding valvular disease were having a mechanical heart valve or any degree of rheumatic mitral stenosis.

The list of participating centers and sub-investigators are presented in Appendix 1.

We planned the present study on behalf of the Young Cardiologists Subgroup of the Turkish Society of Cardiology.

Demographic, clinical, and laboratory characteristics of study participants with their medications used (antiplatelet, anticoagulant, and antiarrhythmic drugs) were obtained through the NOAC-TURK survey database. Additional necessary medical records were obtained from electronic health records of participating centers. The survey included questions about stroke and other embolic adverse events-related risk factors such as coronary heart disease (CHD), hypertension, diabetes mellitus, previous stroke, congestive heart failure (CHF), and vascular disease (prior myocardial infarction, peripheral artery disease). Embolic events were also recorded during the study period. Moreover, hemorrhagic events associated with antiplatelet or anticoagulant drugs were noted. Stroke and thromboembolism risk were assessed using CHA_2DS_2–VASc (CHF or left ventricular dysfunction, hypertension, age ≥75 or 65–74 years, diabetes, thromboembolism or a history of stroke, vascular disease, and sex) and bleeding risk by HAS-BLED (hypertension, renal or liver failure, stroke history, bleeding history, labile INR, age >65 years, drugs predisposing to bleeding, and alcohol use) score (9, 10). Glomerular filtration rate was calculated using the Modification of Diet in Renal Disease (MDRD) formula (11). Chronic renal failure (CRF) was defined as whether or not GFR was estimated to be <60 mL/min. Major bleeding was defined as a fall in hemoglobin level of at least 2 g/dL or requiring two or more units of whole blood/erythrocyte transfusion or symptomatic bleeding in a critical organ/area, such as intracranial, intraocular, intra-spinal, retroperitoneal, intra-articular, pericardial, and intramuscular bleeding, leading to compartment syndrome or fatal, according to International Society on Thrombosis and Hemostasis criteria (12). Minor bleeding was defined as any bleeding other than major bleeding considered to be related to NOACs use. Mortality data were obtained from electronic health records of participating

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centers but were not included in the analysis because of the cross-sectional nature of the study.

The study was approved by the local ethics committee (the Ethics Committee of Haydarpaşa Numune Training and Research Hospital; HNEAH-KAEK 2015/KK/60). Written informed consent was obtained from all study patients.

Statistical analysis

Data were analyzed by Statistical Package for Social Sciences (SPSS) version 17.0 for Windows (IBM, Armonk, New York, USA). Whether or not the distributions of continuous variables were normal was determined by the Kolmogorov–Smirnov test. Data were shown as mean±standard deviation or median (min – max) for continuous variables. Number of cases and percentages were used for categorical data. Mean differences between groups were compared by Student's t-test, whereas the Mann–Whitney U test was applied for comparisons of the not normally distributed data. Categorical variables were analyzed by chi-square or Fisher's exact test, where applicable. Determining the best predictor(s) that affect(s) each clinical outcome (i.e., bleeding, other embolic events) was performed by using the multiple logistic regression backward LR method. Any variable with a p-value <0.25 in a univariate model was accepted as a candidate for the multiple model along with all variables of known clinical importance (13). Odds ratios and 95% confidence intervals for each independent variable were also calculated. Statistical significance was accepted as $p < 0.05$.

Results

In this cross-sectional study, a total of 2.862 patients from 21 different centers of Turkey under the treatment of NOACs for at least three months were included. Baseline demographic and clinical characteristics are summarized in Table 1. The mean age was 70.3±10.2 years, and 60.5% of the study patients were female. The duration of use of NOACs was approximately 10.8±7.6 months.

Eighty-one percent of these patients were hypertensive, 19.8% diabetic, 37.4% had dyslipidemia, and only 18.7% were smokers. The history of these patients showed 26.6% CHF, 7.8% CRF, 11.4% cerebrovascular disease, 6.2% PAD, 2.3% PE, and 2.0% malignancy.

The most common indication for NOACs was permanent AF (83.3%), followed by paroxysmal AF (11.4%), ischemic cerebrovascular disease (3.6%), DVT (2.0%), PE (1.6%), and for prophylaxis following orthopedic surgery.

All patients were evaluated for their CHA_2DS_2-VASc and HASBLED score. The mean value for the CHA_2DS_2-VASc score was 3.4±1.4, and the HASBLED score was 1.8±1.0.

Novel oral anticoagulant drugs were mainly preferred because of an inadequate therapeutic range or overdose during warfarin usage. The second most common reason was physicians' preferences.

Table 1. Baseline characteristics of study patients

Variables	All patients (n=2862)
Age, years	70.3±10.2
Male, %	1131 (39.5)
Female, %	1731 (60.5)
Medical history, %	
Hypertension	2320 (81.1)
Diabetes mellitus	568 (19.8)
Hyperlipidemia	1070 (37.4)
Chronic heart failure	765 (26.7)
Chronic renal failure	224 (7.8)
GFR, mL/min/1.73 m²	78.0±23.1
Cerebrovascular accident	326 (11.4)
Pulmonary embolism	66 (2.3)
Peripheral artery disease	177 (6.2)
Malignancy	58 (2.0)
Smoking	534 (18.7)
Indication for OAC treatment (%)	
Permanent AF	2385 (83.3)
Paroxysmal AF	325 (11.4)
Ischemic stroke	103 (3.6)
Deep vein thrombosis	56 (2.0)
Pulmonary embolism	46 (1.6)
Profylaxis for orthopedic surgery	5 (0.2)
Other	1 (0.0)
Baseline risk analysis	
CHA_2DS_2-VASc score	3.4±1.4
HASBLED score	1.8±1.0

AF - atrial fibrillation; GFR - glomerular filtration rate; OAC - oral anticoagulant

Medical treatment

All patients were evaluated for their NOAC doses and frequencies (Fig.1). Rivaroxaban and dabigatran were both more preferred than apixaban. A lower dose of dabigatran was more preferred than its recommended dose. Almost half of the patients (47.6%) were using lower doses of NOACs, which is definitely much more than expected. When people using low-dose NOACs were compared with the ones using it in the recommended dose, it was observed that they were usually older, females at a high rate, with high CHA_2DS_2-VASc and HASBLED scores and low GFR levels (Table 2). This indicates the tendency of the physicians in Turkey to prefer low-dose treatment in high-risk patients.

Additional antiplatelet drug prescription was detected in 12.9% of the patients. Only 1.8% of this prescription involved clopidogrel, and the others were acetylsalicylic acid in different doses. Since most of these were AF patients, they were also prescribed anti-arrythmic/rate-lowering drugs in addition to NOACs. Two hundred twelve of 2,862 patients (7.4%) were taking antiar-

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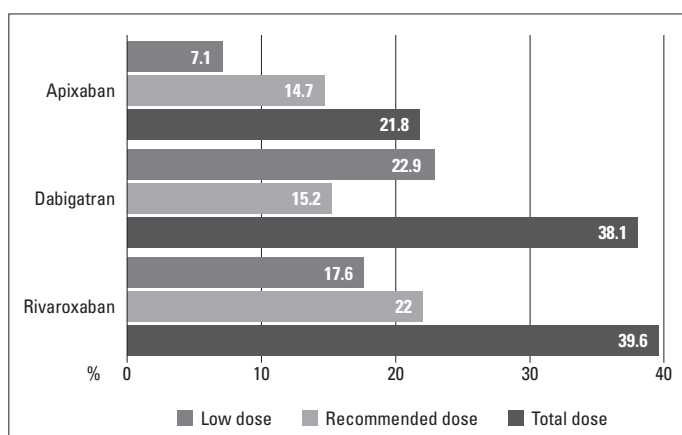
Figure 1. Frequency of the use of each NOAC type and the percentages (prevalence) of the drug use in low and recommended doses among all cases

Table 2. Clinical characteristics of patients using low dose and recommended dose of NOACs

Variables	Low dose (n=1361)	Recommended dose (n=1486)	P
Age, years	74.6±8.9	66.5±9.8	<0.001†
Sex category			0.048‡
Male	513 (37.7%)	614 (41.3%)	
Female	848 (62.3%)	872 (58.7%)	
CRF	162 (11.9%)	61 (4.1%)	<0.001‡
CHA$_2$DS$_2$-VASc score	4 (0–9)	3 (0–9)	<0.001¶
GFR	72.0 (12.2–212.1)	81.0 (1.0–233.0)	<0.001¶
HASBLED score	2 (0–5)	1.5 (0–5)	<0.001¶

†Student's t-test; ‡Chi-square test; ¶Mann–Whitney U test. CRF - chronic renal failure; GFR - glomerular filtration rate

rhythmic/rate control drugs. Among these drugs, beta-blockers (45.5%), non-dihydropyridine calcium channel blockers (12.9%) and digoxin (11.3%) were mainly preferred.

Embolic events

Embolic events including transient ischemic attack, stroke, and peripheral embolism were seen in 37 (1.3%) of the patients (Table 3). NOAC treatment was stopped and warfarin treatment was initiated in 12 patients. NOAC doses were increased in 11 patients and another NOAC treatment was initiated following an embolic event in eight patients. There were no significant differences in terms of the number of patient with embolic complication between with and without additional antiplatelet drug treatment [1.2% (n=30) vs. 1.9% (n=7), p=0.317]. In a univariate analysis, the CVA history and smoking were found to be significant predictors in the group that experienced embolic incident, compared with the group that did not experience it (p=0.003 and p=0.002, respectively) (Table 4). As a result of the univariate statistical analyses, all variables identified as p<0.25 were included in the logistic regression model as candidate risk factors. Multiple logistic regression analysis revealed that

Table 3. Bleeding and embolic complications in patients under NOACs treatment

Complications	Number of patients (n=2862)
Bleeding	217 (7.6%)
Admission count due to bleeding in a year period	1 (1–5)
Bleeding complication in a year period, month	5 (1–33)
Embolism	37 (1.3%)
TIA	17 (0.6%)
Stroke	16 (0.6%)
Peripheral embolism	4 (0.1%)

TIA - transient ischemic attack

Table 4. Demographic and clinical features of groups with and without embolic events

Some variables and comorbidities	Embolism (−) (n=2825)	Embolism (+) (n=37)	P
Age, years	70.3±10.2	73.3±11.0	0.072†
Sex category			0.641‡
Male	1115 (39.5%)	16 (43.2%)	
Female	1710 (60.5%)	21 (56.8%)	
Diabetes mellitus	560 (19.8%)	8 (21.6%)	0.785‡
Hyperlipidemia	1056 (37.4%)	14 (37.8%)	0.954‡
Hypertension	2292 (81.1%)	28 (75.7%)	0.400‡
Deep venous thrombosis	87 (3.1%)	3 (8.1%)	0.109¶
Coronary artery disease	757 (26.8%)	7 (18.9%)	0.282‡
Chronic heart failure	751 (26.6%)	14 (37.8%)	0.124‡
Chronic renal failure	222 (7.9%)	2 (5.4%)	1.000¶
Malignancy	57 (2.0%)	1 (2.7%)	0.533¶
Peripheral artery disease	173 (6.1%)	4 (10.8%)	0.285¶
Pulmonary embolism	64 (2.3%)	2 (5.4%)	0.209¶
Cerebrovascular accident	315 (11.2%)	11 (29.7%)	**0.002¶**
Smoking	520 (18.4%)	14 (37.8%)	**0.003‡**
CHA$_2$DS$_2$-VASC score	3 (0–9)	4 (0–7)	0.199$
GFR, mL/min/1.73 m^2	76.2 (1–233)	82 (42.7–118)	0.158$
HASBLED score	2 (0–5)	2 (0–4)	0.694$
Types of NOACs			
Apixaban	611 (21.7%)	14 (37.8%)	**0.019‡**
Dabigatran	1075 (38.3%)	15 (40.5%)	0.776‡
Rivaroxaban	1124 (40.0%)	8 (21.6%)	**0.023‡**
High-dose NOACs	1474 (52.5%)	12 (32.4%)	**0.015‡**

†Student's t-test; ‡Chi-square test; ¶Fisher's exact test; $Mann–Whitney U test. GFR - glomerular filtration rate; NOACs - new oral anticoagulants

DVT, CVA, smoking, apixaban treatment, and lower doses of NOACs were the main predictors of embolic events in these patients (Table 5). Embolic events with apixaban were significantly higher in these patients, especially in lower doses,

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Table 5. Predictors of embolic events in patients under NOACs treatment

Some risk factors	Odds ratio	95% Confidence interval	P
DVT	4.614	1.328–16.032	0.016
CVA	2.813	1.322–5.982	0.007
Smoking	2.736	1.373–5.453	0.004
Rivaroxaban[a]	1.000	–	–
Apixaban	3.609	1.457–8.941	0.006
Dabigatran	1.720	0.716–4.135	0.225
Low-dose NOACs	2.913	1.385–6.127	0.005

CVA - cerebrovascular accident; DVT - deep vein thrombosis; NOACs - new oral anticoagulants; a - Reference category
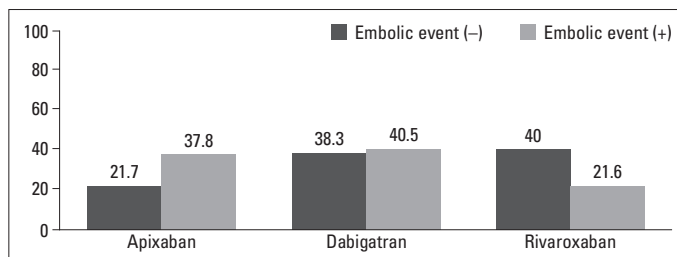
Figure 2. Percentages of NOAC types in the cases that were an embolic incident or not

whereas rivaroxaban was associated with significantly lower embolic events (Fig. 2).

Bleeding

Bleeding complication was seen in 7.6% (217 patients) of these patients (Table 3). The median number of referrals to the hospital due to bleeding in a one-year period was one, and bleeding complication was observed median five months after NOAC prescription. The most common causes for patients being admitted to the hospital were as follows: nasal bleeding (35.0%), hematuria (25.8%), ecchymosis (17.5%), and conjunctival hemorrhage (17.1%). The upper gastrointestinal bleeding (10.6%) and lower gastrointestinal bleeding (10.1%) rates were similar. Major bleeding was observed in 1.1% of the patients. Intracranial bleeding was observed in two patients (0.9%). Bleeding complications were minor in most of the patients such that 68.2% of these patients were treated in outpatient clinics. 31.8% of these patients were treated hospitalized. Fresh frozen plasma was needed in 16.6% of the patients, prothrombin complex in 1.8%, and erythrocyte suspension in 15.7%. Hemodialysis was used in only one patient (0.5%) for bleeding.

In the univariate analysis, the average age (71.6±9.7 vs. 70.2±10.2) of the group in which bleeding was observed was significantly higher; the DM was lower; and hyperlipidemia, PAD, and smoking were high. The CHA$_2$DS$_2$-VASc score (3.5±1.2 vs. 3.3±1.4; p=0.023) and HASBLED (2.2±1.1 vs. 1.8±0.99) score of the group in which bleeding was observed were significantly higher (Table 6). As a result of the univariate statistical analyses, all variables identified as p<0.25 were included in the logistic regression model as candidate risk factors.

Table 6. Demographic and clinical features of groups with and without bleeding

| Some risk factors	Bleeding (+) (n=2645)	Bleeding (–) (n=217)	P
Age, years	70.2±10.2	71.7±9.8	0.048[†]
Sex category			0.406[‡]
Male	1051 (39.7%)	80 (36.9%)	
Female	1594 (60.3%)	137 (63.1%)	
Diabetes mellitus	537 (20.3%)	31 (14.3%)	0.033[‡]
Hyperlipidemia	941 (35.6%)	129 (59.4%)	<0.001[‡]
Hypertension	2140 (80.9%)	180 (82.9%)	0.460[‡]
Deep venous thrombosis	84 (3.2%)	6 (2.8%)	0.739[‡]
Coronary artery disease	705 (26.7%)	59 (27.2%)	0.864[‡]
Chronic heart failure	700 (26.5%)	65 (30.0%)	0.264[‡]
Chronic renal failure	211 (8.0%)	13 (6.0%)	0.295[‡]
Malignancy	53 (2.0%)	5 (2.3%)	0.800[¶]
Peripheral artery disease	127 (4.8%)	50 (23.0%)	<0.001[‡]
Pulmonary embolism	61 (2.3%)	5 (2.3%)	0.998[‡]
Cerebrovascular accident	296 (11.2%)	30 (13.8%)	0.240[‡]
Smoking	463 (17.5%)	71 (32.7%)	<0.001[‡]
CHA$_2$DS$_2$-VASC score	3 (0–9)	4 (1–7)	0.023[$]
GFR, mL/min/1.73 m^2	77 (1–217.3)	76 (25–233)	0.542[$]
HASBLED score	2 (0–5)	2 (0–5)	<0.001[$]
NOAC			
Apixaban	599 (22.8%)	26 (12.0%)	<0.001[‡]
Dabigatran	1001 (38.0%)	89 (41.2%)	0.359[‡]
Rivaroxaban	1031 (39.2%)	101 (46.8%)	0.029[‡]
High-dose NOACs	1364 (51.8%)	122 (56.5%)	0.190[‡]

†Student's t-test; ‡Chi-square test; ¶Fisher's exact test; $Mann–Whitney U test. GFR - glomerular filtration rate; NOAC - new oral anticoagulant

Table 7. Predictors of bleeding in patients under NOACs treatment

	Odds ratio	95% Confidence interval	P
Diabetes mellitus	0.557	0.370–0.839	0.005
Hyperlipidemia	1.873	1.376–2.551	<0.001
PAD	3.396	2.276–5.065	<0.001
Smoking	1.781	1.282–2.472	<0.001
HAS-BLED score	1.426	1.225–1.659	<0.001
Apixaban[a]	1.000	–	–
Dabigatran	2.233	1.389–3.590	<0.001
Rivaroxaban	2.325	1.463–3.697	<0.001
High-dose NOACs	1.530	1.126–2.078	0.006

a-reference category; NOACs - new oral anticoagulants; PAD - peripheral artery disease

Logistic regression analysis revealed that a lack of diabetes mellitus, dyslipidemia, PAD, smoking, higher HASBLED score,

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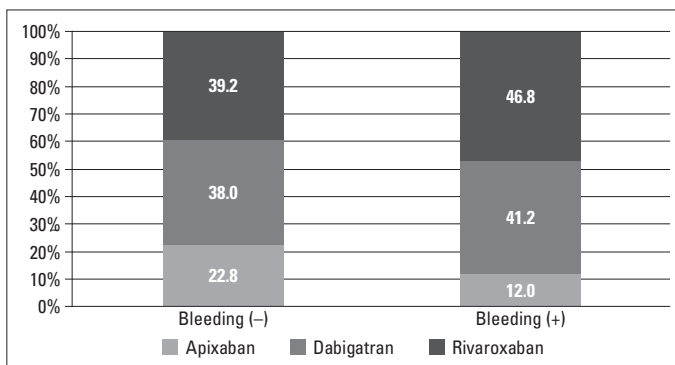
Figure 3. Percentages (prevalence) of NOAC types used in the cases with or without bleeding: cumulative bar graph

dabigatran and rivaroxaban treatment, and higher doses of NOACs were the main predictors for bleeding (Table 7). While bleeding with rivaroxaban was significantly higher especially in high doses in these patients, apixaban was related with significantly lower bleeding rates, especially in higher doses (Fig. 3).

Discussion

NOAC-TURK is the first study to report the efficacy and safety of NOACs for all indications, including NVAF, DVT, and PE, in the same study in Turkey. There are many important main findings in this study. First, this study reported that the most common indication for NOACs use in Turkey was permanent AF, which is concordant with large current observational studies (8, 14–16). Another important finding was that nearly half of the study participants were using reduced doses of NOACs, which is discordant with recent phase-III trials and clinical studies (17–19).

In the ARISTOTLE study, reduced doses of apixaban were given to patients with an age of at least 80 years, body weight of no more than 60 kg, or a serum creatinine level of 1.5 mg/dl or more. A 2.5-mg dose of apixaban was administered to only 4.7% of the patients in the ARISTOTLE study; however, 7.1% of the patients in the present study used lower doses of apixaban, which means that almost one-third of all patients were using apixaban (19).

Bleeding is an important life-threatening complication of NOACs use. In the present study, the major bleeding rate was 1.1% and both major and minor bleeding complications were seen in 7.6% of the patients, which is less than the figure in large clinical trials (17–19). Less bleeding complications may be related to the cross-sectional design of the study as well as increased use of lower doses of NOACs. Minor bleeding events occurred more commonly than major events such as intracranial or gastrointestinal sites. Detailed dose and drug relation showed that bleeding with rivaroxaban was significantly higher, especially in recommended doses in patients with AF, and apixaban was related with significantly lower bleeding rates, especially in recommended doses. Diabetes mellitus, dyslipidemia, PAD, smoking, higher HAS-BLED score, dabigatran and rivaroxaban treatment, and higher doses of NOACs were the main predictors for bleeding, which also confirms HAS-BLED score efficiency. Bleeding

events occurred in 7.6% of the patients in the NOAC-TURK study, which is similar to the results of the one-year follow up of the EORP-AF study (8.4%) (15). However, the number of bleeding events increased to 11% in the EORP-AF study in the second-year follow up. A lower dosage of NOAC usage could be the reason of facing lower number of bleeding events in our study.

The incidence of embolic events was which is less than previous large clinical trials (17–19). Embolic events with apixaban were significantly higher in these patients, especially in lower doses, whereas rivaroxaban was related with significantly lower embolic events. Logistic regression analysis for predicting embolic complication revealed that apixaban and lower doses of NOACs treatment were two important main predictors. Larsen et al. (20) showed that compared with warfarin, rivaroxaban was related to lower embolic events, and dabigatran and apixaban had similar rates with warfarin. One-year embolic event rates were the highest (4.86%) in the apixaban group in their nationwide cohort study. The embolic event rate was higher in the apixaban group, but it was only 2.24% in our study. The EORP-AF study (15) had higher incidences for embolic events—9.1% for the first-year follow up and 11.6% for the second-year follow up—whereas only 1.3% of our study population had embolic events. We therefore suggested that low embolic complication rate may be due to a lack of follow-up data in our study. Moreover, a heightened effect of apixaban for embolic complications in multiple analyses was due to a high incidence of use of lower doses in all indications.

This study supports the widespread use of NOACs for the prevention of embolic complications in the case of NVAF, DVT, and PE in the daily practice of cardiologists in our country. The RAMSES (8) and the AFTER (14) studies are other large-scale, important cross-sectional observational studies on Turkish populations. Moreover, the NOAC-TURK study, which gives incremental data for the prevention of embolic complications, has some unique features, including both cross-sectional and short-term follow-up data with more wide indications.

The mean age and female dominance were the same as previous observational studies (8, 14–16). Hypertension was the most common etiology for NVAF, which was concordant with previous observational studies (8, 14–16) and randomized controlled trials (17–19). However, the previous incidence of stroke or TIA was lower than both the RAMSES and AFTER studies (8, 14). Permanent AF was the most common indication for prescribing NOACs in our study, which is similar to previous observational studies (8, 14–16). The reason for this majority of AF indication could be because this study was conducted in cardiology clinics. The mean CHA_2DS_2-VASc score was similar to the RAMSES and the AFTER studies (8, 14).

The disadvantages of warfarin lead to a decreased use of OAC therapy worldwide (8). While a single center study reported a 30.1% incidence of OAC use for AF (21), a tertiary center study presented increased data (67.3%) (22). The RAMSES and the AFTER studies reported incidences for OAC of 72% and 40%, respec-

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tively (8, 14). In our study, the rate of previous warfarin use was 48.6% and dabigatran 110 mg was the most commonly prescribed NOAC in patients with NVAF. The main reason for switching warfarin to NOACs may be because of practicability and strong preventive evidence of these new drugs in NVAF patients. Concordant with previous studies, NOACs were preferred over warfarin for embolic complications in patients with NVAF in this study, despite recently emerging in the market of these drugs. Moreover, as with the RAMSES study (8), dabigatran was the most frequently used NOAC in our study, followed by rivaroxaban and apixaban. The highest incidence of dabigatran could be because it was the first NOAC registered by the Ministry of Health in Turkey. However, interestingly, discordant with other previous studies, a 110-mg dose of dabigatran was preferred more frequently than a 150-mg dose for NVAF patients in our population. While a 2.5-mg dose of apixaban was used in only 4.7% of the patients in the ARISTOTLE study (19), 7.1% of the patients in the present study—almost one-third of all patients—used low-dose apixaban. Limited RCT and observational data about efficacy and safety of NOACs may affect physicians' choice toward a low-dose regimen in the setting of NVAF in our study, which is different from previous studies.

The patients who were on antiplatelet therapy for stable CHD, chronic ischemic heart disease had increased CHA_2DS_2-VASc and HASBLED scores, which is a big concern in terms of bleeding risk in using NOAC in the setting of AF. Hence, the need for combination therapy should be assessed according to risk–benefit considerations. In our study, the rate of combination therapy was lower than that in previous studies (8, 14–16), which was detected in 12.9% of the patients.

The concomitant use of all rate control/lowering drugs (beta-blockers, non-dihydropridine calcium channel blockers, and digoxin) were higher in the AFTER (14) and RAMSES (8) study populations compared with that in our study's population (45.5%, 58.7%, 63.3% for beta-blockers; 12.9%, 23.4%, 23.6% for non-dihydropyridine calcium channel blockers; and 11.3%, 27.7%, 20.5% for digoxin usage, respectively, for the NOAC-TURK, AFTER, and RAMSES studies). Moreover, while the concomitant usages of beta-blockers and digoxin are higher in the EORP (15) study, non-dihydropyridine calcium channel blockers and digoxin usages were higher in the NOAC-TURK study.

In the AFTER study (14), the investigators found that only 41.3% of the population had effective INR levels. Furthermore, the mean time in therapeutic range reported 40.5% in RAMSES study (8). We also found that patients are treated with lower doses than clinically indicated. The most common cause was physicians' neglect in the AFTER study for inadequate anticoagulation; in the NOAC-TURK study, misjudgment of patients' clinical status could be the reason of treating patients with lower doses.

Study limitations

There are some limitations in our study. Since this study has a cross-sectional design, which is a snapshot of study participants' characteristics, it could not provide any data in terms of mortality and future embolic and bleeding adverse events. Moreover, the enrollment of patients was limited to only outpatient cardiology clinics. Hence, this study's results do not extrapolate to all Turkish NOAC-using patients for different indications.

Conclusion

In conclusion, this multicenter cross-sectional study showed an important overview of the current NOACs treatment regimens in Turkey. Although embolic and bleeding complications are lower or similar to various studies, increased utilization of lower doses in this study should be addressed carefully. According to the results of this study, NOACs treatment should be guided through CHA_2DS_2-VASc and HASBLED scores to ensure more benefit and less adverse effects in NVAF patients.

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References

1. Pistoia F, Sacco S, Tiseo C, Degan D, Ornello R, Carolei A. The epidemiology of atrial fibrillation and stroke. Cardiol Clin 2016;34:255-68.
2. Uyarel H, Onat A, Yüksel H, Can G, Ordu S, Dursunoğlu D. Incidence, prevalence and mortality estimates for chronic atrial fibrillation in Turkish adults. Arch Turk Soc Cardiol 2008; 36: 214-22.
3. Anderson FA Jr, Wheeler HB, Goldberg RJ, Hosmer DW, Patwardhan NA, Jovanovic B, et al. A population-based perspective of the hospital incidence and case-fatality rates of deep vein thrombosis and pulmonary embolism. The Worcester DVT Study. Arch Intern Med 1991; 151: 933-8. [CrossRef]
4. Huang W, Goldberg RJ, Anderson FA, Kiefe CI, Spencer FA. Secular trends in occurrence of acute venous thromboembolism: the Worcester VTE study (1985–2009) Am J Med 2014; 127: 829-39.e5.
5. Rothwell PM, Coull AJ, Giles MF, Howard SC, Silver LE, Bull LM, et al. Change in stroke incidence, mortality, case-fatality, severity, and risk factors in Oxfordshire, UK from 1981 to 2004 (Oxford Vascular Study). Lancet 2004; 363: 1925-33. [CrossRef]
6. Koton S, Schneider AL, Rosamond WD, Shahar E, Sang Y, Gottesman RF, et al. Stroke incidence and mortality trends in US communities, 1987 to 2011. JAMA 2014; 312: 259-68. [CrossRef]
7. Bassand JB, Accetta G, Camm AJ, Cools F, Fitzmaurice DA, Fox KAA, et al. Two-year outcomes of patients with newly diagnosed atrial fibrillation: results from GARFIELD-AF. Eur Heart J 2016 Jun 29. [CrossRef]
8. Başaran O, Beton O, Doğan V, Tekinalp M, Aykan AC, Kalaycıoğlu E, et al. ReAl-life Multicenter Survey Evaluating Stroke prevention strategies in non-valvular atrial fibrillation (RAMSES study). Anatol J Cardiol 2016; 16: 734-41. [CrossRef]
9. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the Euro Heart Survey on atrial fibrillation. Chest 2010; 137: 263-72. [CrossRef]
10. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. Chest 2010; 138: 1093-100. [CrossRef]
11. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med 1999; 130: 461-70.
12. Schulman S, Kearon C. Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thombosis and Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost 2005; 3: 692-4.
13. Hosmer D, Lemeshow S, May S. Model Building Strategies and Methods for Logistic Regression. In: Hosmer D, editor. Applied Logistic Regression. 2nd ed. New Jersey: John Wiley & Sons, Inc. Canada; 2000. p.91-142. [CrossRef]
14. Ertaş F, Kaya H, Yüksel M, Soydinç MS, Alan S, Ülgen MS. Atrial Fibrillation in Turkey: Epidemiologic Registry (AFTER) study design. Anatol J Cardiol 2013; 13: 339-43. [CrossRef]
15. Lip GY, Laroche C, Dan GA, Santini M, Kalarus Z, Rasmussen LH, et al. A prospective survey in European Society of Cardiology member countries of atrial fibrillation management: baseline results of EURObservational Research Programme Atrial Fibrillation (EORP-AF) Pilot General Registry. Europace 2014; 16: 308-19. [CrossRef]
16. Proietti M, Laroche C, Opolski G, Maggioni AP, Boriani G, Lip GY; AF Gen Pilot Investigators. 'Real-world' atrial fibrillation management in Europe: observations from the 2-year follow-up of the EURObservational Research Programme-Atrial Fibrillation General Registry Pilot Phase. Europace 2016 May 18. [CrossRef]
17. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. and *the RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009; 361: 1139-51. [CrossRef]
18. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, and the ROCKET AF Steering Committee, for the ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011; 365: 883-91. [CrossRef]
19. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, et al for the ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2011; 365: 981-92. [CrossRef]
20. Larsen TB, Skjøth F, Nielsen PB, Kjældgaard JN, Lip GY. Comparative effectiveness and safety of non-vitamin K antagonist oral anticoagulants and warfarin in patients with atrial fibrillation: propensity weighted nationwide cohort study. BMJ 2016 Jun 16; 353: i3189. doi: 10.1136/bmj.i3189. [CrossRef]
21. Karacaglar E, Atar I, Yetis B, Corut H, Ersoy B, Yilmaz K, et al. The frequency of embolic risk factors and adequacy of anti-embolic treatment in patients with atrial fibrillation: A single tertiary center experience. Anatol J Cardiol 2012; 12: 384-90. [CrossRef]
22. Ertas F, Duygu H, Acet H, Eren NK, Nazli C, Ergene AO. Oral anticoagulant use in patients with atrial fibrillation. Arch Turk Soc Cardiol 2009; 37: 161-7.

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Appendix 1. Participating researchers and centers in the NOAC-TURK study (in order of city name)

Researcher's name	Center	Province	Patient number
Çağrı Yayla	Yüksek İhtisas Training and Research Hospital	Ankara	78
Mehmet Kadri Akboğa			35
Serkan Ünlü	Gazi University Faculty of Medicine	Ankara	168
Uğur Canpolat	Hacettepe University Faculty of Medicine	Ankara	100
Bayram Köroğlu	Bingöl State Hospital	Bingöl	83
Gürkan Karaca	Osmancık State Hospital	Çorum	47
Fatih Mehmet Uçar	Denizli State Hospital	Denizli	105
Servet Altay	Edirne State Hospital	Edirne	256
Lütfü Aşkın	Palandöken State Hospital	Erzurum	230
Özge Özden Tok	Bakırköy Sadi Konuk Training and Research Hospital	İstanbul	191
Ümit Yaşar Sinan	İstanbul University, Cardiology Institute	Istanbul	197
Mehmet Emin Kalkan	Kartal Koşuyolu Training and Research Hospital	İstanbul	65
Mehmet Erdem Memetoğlu	Dr. Siyami Ersek Thoracic and Cardiovascular Surgery	İstanbul	10
Yalçın Velibey	Training and Research Hospital		73
Kazım Serhan Özcan	Derince Training and Research Hospital	Kocaeli	77
Halil İbrahim Erdoğan	NEU University, Meram Medical Faculty	Konya	6
Hüseyin Altuğ Çakmak	Kaçkar State Hospital	Rize	255
Hakan Duman	Recep Tayyip University, Faculty of Medicine	Rize	101
Okan Gülel	Ondokuz Mayıs University, Faculty of Medicine	Samsun	101
Ömer Gedikli			150
Ahmet Yanık	Samsun Training and Research Hospital	Samsun	131
Feyzullah Beşli	Harran University, Faculty of Medicine	Şanlıurfa	200
Fatma Özpamuk Karadeniz	Balıklıgöl State Hospital	Şanlıurfa	172
Serkan Akdağ	Yüzüncü Yıl University, Faculty of Medicine	Van	31