Real-life data of major and minor bleeding events with direct oral anticoagulants in the one-year follow-up period: The NOAC-TURK study

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Abstract

Objective: This study aimed to evaluate the safety of direct oral anticoagulants (DOACs) in patients with non-valvular atrial fibrillation (NVAF) during daily clinical practice.

Methods: This was a prospective study conducted between January 01, 2016, and April 01, 2017, in patients aged ≥18 years with a diagnosis of NVAF. We performed the study in 9 clinical centers from different regions of Turkey, and the mean follow-up period was 12+2 months. We investigated major and minor bleeding events of DOAC.

Results: A total of 1807 patients with NVAF were enrolled. The mean age of the patients was 73.6±10.2 years, CHA2DS2-VASc score was 3.6±1.4, and HAS-BLED score was 2±1.2. The most frequently prescribed DOAC was dabigatran 110 mg bid in 409 (22.6%) patients. The patients on apixaban 2.5 mg bid were older (p<0.001). Patients on rivaroxaban 15 mg od also had a higher prevalence of chronic renal failure, 46 (16.7%) patients. A total of 205 (11.4%) bleeding events were observed; among these, 34 (1.9%) patients had major bleeding and 171 (9.4%) patients had minor bleeding. The major and minor bleeding events were 2/273 (0.7%) and 30/273 (10.9%) in patients receiving dabigatran 150 mg bid, 13/409 (3%) and 44/409 (10.7%) in patients receiving dabigatran 110 mg bid, 4/385 (1%) and 42/385 (10.9%) in patients receiving rivaroxaban 20 mg od, 8/276 (2.9%) and 27/276 (9.7%) in patients receiving rivaroxaban 15 mg od, 3/308 (0.9%) and 14/308 (4.5%) in patients receiving apixaban 5 mg bid, 4/156 (2.5%) and 14/156 (9%) in patients receiving apixaban 2.5 mg bid, respectively. The total bleeding events were 17 (5.6%) in patients receiving apixaban 5 mg, less than those receiving other DOACs. On multivariate analyses, rivaroxaban 20 mg od (p=0.002), ATRIA and HAS-BLED scores, and peripheral artery disease were independent indicators of bleeding. The most frequent location of major bleeding was the gastrointestinal system (GIS) [17 (0.9%) patients], and the most frequent location of minor bleeding was the gingiva [45 (2.5%) patients].

Conclusion: This study showed that similar results as the previous real-life study; however, we had some different results, such as the GIS tract bleeding was more frequent in patients receiving dabigatran 110 mg bid. The major and intracranial bleeding events were similar for different DOACs; and among DOACs, only rivaroxaban 20 mg od was associated with a high risk of bleeding.

Key words: direct oral anticoagulants, major bleeding, minor bleeding, real-life data, non-valvular atrial fibrillation

Cite this article as: *Gedikli Ö, Altay S, Ünlü S, Çakmak HA, Aşkın L, Yanık A, et al. Real-life data of major and minor bleeding events with direct oral anticoagulants in the one-year follow-up period: The NOAC-TURK study. Anatol J Cardiol 2021; 25: 196-204.*

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Accepted Date: 08.01.2021 **Available Online Date:** 22.02.2021

DOI:10.5152/AnatolJCardiol.2021.57635

HIGHLIGHTS

- A total of 205 (11.4%) bleeding events were observed in patients on direct oral anticoagulants (DOACs).
- Rivaroxaban 20 mg once daily was an independent indicator of bleeding.
- Reduced dosage of DOACs is associated with higher bleeding rates.
- Peripheral artery disease was associated with bleeding in this study.
- Major and intracranial bleeding events were similar for different DOACs.

Introduction

Atrial fibrillation (AF) is the most common arrhythmia diagnosed in clinical practice (1). Anticoagulation is the essential therapy for the management of AF, and anticoagulation treatment strategy should be applied according to CHA2DS2-VASc scoring system in patients with non-valvular AF (NVAF) (2). The effectiveness and safety of direct oral anticoagulants (DOACs) have been proved in previous studies; nevertheless, bleeding is a serious and common side effect of DOACs (3-5). DOACs may cause bleeding, which can vary from minor bleeding to major bleeding or life-threatening intracranial hemorrhages (3-7). The new oral anticoagulants-Turkey (NOAC-TURK) study has reported bleeding and ischemic events in patients using DOACs in Turkey (8). Despite having a retrospective analysis of the association between bleeding risk and DOAC-related events (9-11), no prospective study with at least 1-year follow-up of real-life data has been conducted yet. Therefore, this study aimed to investigate the major and minor bleeding event rates, sites, and management in patients with the indication of NVAF treated with DOACs.

Methods

This study was designed by the young cardiologists of Turkey with an aim to prospectively investigate DOAC-related bleeding events in a 1-year follow-up of patients with NVAF who participated in the NOAC-TURK study. The DOAC regimen and treatment duration differ for NVAF, deep venous thrombosis (DVT), and pulmonary thromboembolism (PTE) (12). A total of 1,807 patients from 9 centers were followed prospectively. The number of participants was less than those in the NOAC-TURK study. A total of 10 centers did not participate in the follow-up study owing to the change in the clinic center and the position of the investigator, 20 patients were lost to follow-up, and the patients receiving DOACs with indications of DVT and PTE were excluded.

The study was conducted between January 01, 2016, and April 01, 2017. Patients older than 18 years with a diagnosis of NVAF and indication for DOACs were included. Any contraindication to the usage of DOAC was accepted as exclusion criteria. The follow-up of the patients was performed face to face or via a telephone interview. Any history of hypertension, chronic kidney disease, coronary artery disease (history of percutaneous intervention or coronary artery bypass graft surgery), peripheral artery disease (PAD), diabetes mellitus, congestive heart failure, and valvular disorders (any degree of mitral regurgitation, aortic stenosis, or aortic regurgitation) were recorded. Demographic, clinical, and laboratory characteristics of the study participants were obtained via the NOAC-TURK survey database. If available, new clinical and laboratory parameters were added to the database. Medical records required for the study were obtained from the participating centers via electronic file transfers. The medical records included the occurrence of new clinical events or diagnoses, such as stroke and other embolic adverse events, coronary heart disease, hypertension, diabetes mellitus, congestive heart failure, and vascular disease (prior myocardial infarction, PAD). CHA2DS2-VASc, HAS-BLED, and ATRIA scores of patients were re-calculated (13-15). Modification of diet in renal disease (16) was used for calculating the glomerular filtration rate (GFR). Chronic renal failure (CRF) was defined as having a GFR<60 mL/min. Major bleeding was defined as a decrease in the hemoglobin level of at least 2 g/dL or requiring 2or more units of whole blood/erythrocyte transfusion or symptomatic bleeding in a critical organ/area according to the international society on thrombosis and hemostasis criteria (17). Minor bleeding was characterized as any sign or symptom of hemorrhage and clinically relevant bleeding without major bleeding that was considered to be related to DOACs use. Symptomatic and clinically relevant gingival bleeding was considered in this study. Temporary discontinuation was defined as an interruption of DOACs for shorter than 4 weeks without the initial plan.

The Local Ethics Committee approval was obtained (the Ethics Committee of Haydarpaşa Numune Training and Research Hospital; HNEAH-KAEK 2015/KK/60). Informed consent was obtained from all participants.

Statistical analysis

Continuous variables were presented as mean ± standard deviation, and categorical data were presented as percentages or frequencies. Continuous variables were examined by the Kolmogorov–Smirnov test to check for normality of distribution. Categorical variables were compared by the χ^2 test.

The patient population was categorized on the basis of the type of DOAC and bleeding status. Baseline characteristics were compared among groups using the Student's t-test or one-way analysis of variance (ANOVA) test. Significant determinants of bleeding were determined via the Cox proportional hazard model with a backward stepwise likelihood ratio. Clinical variables, including age, sex, type of DOAC, and CHA2DS2-VASc, HAS-BLED, ATRIA scores were analyzed in a multivariable model. Sex, type of DOAC, and having comorbidities were encoded as categorical variables, and the remaining were encoded as continuous variables. The significance level for a

Anatol J Cardiol 2021; 25: 196-204
DOI:10.5152/AnatolJCardiol.2021.57635

Table 1. Baseline characteristics of study patients

Characteristics	Dabigatran 150 mg bid (n=273)	Dabigatran 110 mg bid (n=409)	Rivaroxaban 20 mg od (n=385)	Rivaroxaban 15 mg od (n=276)	Apixaban 5 mg bid (n=308)	Apixaban 2.5 mg bid (n=156)	Total (n=1.807)	*P*
Age (years) (mean±SD)	68.7±9.4	76.5±9.5*	69.2±10.5$^{\#\Omega}$	77.7±9*	72.2±9.2$^{*\#\Omega\pi\infty}$	81.6±6$^{*\#\Omega\pi}$	73.6±10.2	<0.001
Female, n (%)	165 (60.4)	247 (60.5)	232 (60.7)	166 (60.1)	190 (61.9)	106 (68.4)	1.106 (61.4)	0.591
Previous stroke, TIA, n (%)	40 (14.7)	54 (13.2)	36 (9.4)	38 (13.8)	27 (8.8)	18 (11.5)	213 (11.8)	0.113
Diabetes mellitus, n (%)	64 (23.4)	105 (25.7)	71 (18.4)	43 (15.6)	65 (21.1)	34 (21.8)	382 (21.1)	0.026
Hyperlipidemia, n (%)	127 (46.5)	199 (48.7)	179 (46.5)	116 (42)	132 (42.9)	69 (44.2)	822 (45.5)	0.518
Hypertension, n (%)	231 (84.6)	366 (89.5)	304 (79)	250 (90.6)	261 (84.7)	146 (93.6)	1558 (86.2)	<0.001
Coronary artery disease, n (%)	57 (20.9)	101 (24.7)	91 (23.6)	84 (30.4)	89 (28.9)	61 (39.1)	483 (26.7)	<0.001
Chronic heart failure, n (%)	61 (22.3)	111 (27.1)	101 (26.2)	97 (35.1)	91 (29.6)	61 (39.1)	522 (28.9)	0.001
Chronic renal failure, n (%)	9 (3.3)	42 (10.3)	18 (4.7)	46 (16.7)	29 (9.4)	23 (14.7)	167 (9.2)	<0.001
Peripheral artery disease, n (%)	28 (10.3)	43 (10.5)	36 (9.4)	22 (8)	13 (4.2)	9 (5.8)	151 (8.4)	0.028
CHA2DS2-VASC score, n (%)	3.2±1.3	3.9±1.4*	3.2±1.3$^{\#\Omega}$	4±1.4*	3.3±1.3$^{\#\Omega\infty}$	4±1.3$^{*\pi}$	3.6±1.4	<0.001
GFR (mL/min/1.73 m^2)	83.9±21.9	74.1±19.9*	81.3±21.3$^{\#\Omega}$	72±21.4*	82.4±20.9$^{\#\Omega\infty}$	74.6±19.1$^{*\pi}$	78.3±21.3	<0.001
HAS-BLED score	1.9±1	2.2±1.5*	1.9±1.1$^{\#\Omega}$	2.4±1.1*	1.7±1$^{\#\Omega\infty}$	2.2±1.1$^{*\pi}$	2±1.2	<0.001
ATRIA	6.2±6.3	4.8±4.5*	4.4±3.7$^{*\Omega}$	5.6±3.4	3.9±2.9$^{*\Omega}$	4±2.7$^{*\Omega}$	4.8±4.3	<0.001
ASA, n (%)	17 (6.2)	28 (6.9)	21 (5.5)	19 (6.9)	28 (9.1)	19 (12.2)	132 (7.3)	0.089
Clopidogrel, n (%)	2 (0.7)	9 (2.2)	4 (1)	2 (0.7)	6 (2)	8 (5.1)	31 (1.7)	0.008
APTT (s)	40.1±13.1	36.9±8	37.3±7.1	63.3±89.3	34.9±8.2	33.4±9.8	41.8±39.5	0.188
Platelets (mcL)	209,466.7± 84,361.4	225,027± 85,955.6	196,096.8± 84,529.4	230,869.6± 76,778.5	239,642.9± 74,523.7	220,352.9± 57,490.2	218,671.5± 79,656.2	0.493
INR	1.7±1.2	1.5±0.3	1.6±0.8	2.6±3.6	1.3±0.4	1.5±0.6	1.7±1.6	0.127

ANOVA test was used for continuous variables with post-hoc Bonferroni correction. Categorical variables were compared by the χ^2 test. For post-hoc analysis, results are shown as; *significantly different from dabigatran 150 mg, $^{\#}$and dabigatran 110 mg group, $^{\Omega}$significantly different from rivaroxaban 15 mg group, and $^{\pi}$rivaroxaban 20 mg group, $^{\infty}$significantly different from apixaban 2.5 mg group. GFR - glomerular filtration rate; ASA - acetylsalicylic acid; SD - standard deviation. TIA - transient ischemic attack; INR - international normalized ratio

variable to remain in the multivariable model was 0.05, and the exclusion criterion was 0.10. A two-tailed p-value of <0.05 was considered statistically significant. All the data were analyzed using the Statistical Package for Social Sciences version 23.0.

Results

A total of 1,807 patients with NVAF were enrolled. Demographic characteristics of the study population are presented in Table 1. Of the patients, 409 (22.6%) were prescribed dabigatran 110 mg bid, which was the most frequently prescribed DOAC; followed by rivaroxaban 20 mg od, which was prescribed to 385 (21.3%) patients; and apixaban 5 mg prescribed to 308 (17%) patients. Patients who were on dabigatran 150 mg and rivaroxaban 20 mg od therapies were younger (p<0.001, ANOVA) with better glomerular filtration rate and CHA2DS2-VASc and HAS-BLED scores (all p<0.001, ANOVA). The patients on apixaban 2.5 mg bid therapy had the highest mean age compared with other groups (p<0.001, ANOVA). Moreover, they had a more common prevalence of coronary artery disease [61 (39.1%) patients] and chronic renal disease [23 (14.7%) patients]. Patients on rivaroxaban 15 mg od also had a higher prevalence of chronic renal disease [46 (16.7%) patients].

In this study, 205 (11.4%) bleeding events were observed; among these, 34 (1.9%) patients had major bleeding and 171 (9.4%) patients had minor bleeding. The major and minor bleeding events were 2/273 (0.7%) and 30/273 (10.9%) on dabigatran 150 mg bid, 13/409 (3%) and 44/409 (10.7%) on dabigatran 110 mg bid, 4/385 (1%) and 42/385 (10.9%) in rivaroxaban 20 mg od, 8/276 (2.9%) and 27/276 (9.7%) on rivaroxaban 15 mg od, 3/308 (0.9%) and 14/308 (4.5%) in apixaban 5 mg bid, and 4/156 (2.5%) and 14/156 (9%) in apixaban 2.5 mg bid, respectively (Table 2).

Baseline demographic and clinical characteristics according to having a bleeding event are presented in Table 3. Patients who experienced a bleeding event were older and had higher CHA2DS2-VASC, HAS-BLED, and ATRIA scores along with hyperlipidemia, PAD, and lower GFR (all p<0.001, ANOVA). The multiple Cox regression analyses are presented in Table 4 and reveals that rivaroxaban 20 mg od [hazard ratio (HR)=1.760, 95% confidence interval (CI): 1.228–2.524, p=0.002] is independently associated with bleeding among DOAC groups. The other significant independent parameters associated with bleeding were found to be high ATRIA and HAS-BLED scores and having PAD (Table 4).

Table 2. Major and minor bleeding events of DOACs

Variables	Dabigatran 150 mg bid (n=273)	Dabigatran 110 mg bid (n=409)	Rivaroxaban 20 mg od (n=385)	Rivaroxaban 15 mg od (n=276)	Apixaban 5 mg bid (n=308)	Apixaban 2.5 mg bid (n=156)	Total (n=1.807)	*P*
Total bleeding, n (%)	32 (11.7)	57 (13.9)	46 (12)	35 (12.7)	17 (5.6)	18 (11.5)	205 (11.4)	0.018
Major bleeding, n (%)	2 (0.7)	13 (3)	4 (1)	8 (2.9)	3 (0.9)	4 (2.5)	34 (1.9)	0.182
Minor bleeding, n (%)	30 (10.9)	44 (10.7)	42 (10.9)	27 (9.7)	14 (4.5)	14 (9)	171 (9.4)	

Table 3. Demographic and clinical features of groups with and without bleeding

Characteristic	Patients without bleeding (n=1.602)	Patients with bleeding (n=205)	*P*
Age (years) (mean±SD)	73.3±10.2	76.6±10.2	<0.001
Female, n (%)	983 (61.1)	130 (63.4)	0.290
Previous stroke TIA, n (%)	186 (11.5)	31 (15)	0.170
Diabetes mellitus, n (%)	341 (21)	47 (22.7)	0.528
Hyperlipidemia, n (%)	712 (44)	122 (58.9)	<0.001
Hypertension, n (%)	1399 (86.4)	178 (86)	0.914
Coronary artery disease, n (%)	421 (26)	66 (31.9)	0.079
Chronic heart failure, n (%)	468 (28.9)	56 (27.1)	0.625
Chronic renal failure, n (%)	140 (8.6)	29 (14)	0.015
Peripheral artery disease, n (%)	124 (7.7)	30 (14.5)	0.001
CHA2DS2-VASC score	3.5±1.4	4±1.5	<0.001
GFR, mL/min/1.73 m^2	79.1±21	70.9±22.6	<0.001
HAS-BLED score	2±1	2.5±1.1	<0.001
ATRIA	4.6±4.2	6.6±4.7	<0.001
ASA, n (%)	114 (7)	19 (9.2)	0.164
Clopidogrel, n (%)	29 (1.8)	2 (1)	0.300

Student t-test was used to compare groups according to bleeding status. GFR - glomerular filtration rate; ASA - acetylsalicylic acid; TIA - transient ischemic attack

The sites of major and minor bleeding and management of bleeding events are summarized in Table 3. There was a significant difference in the rates of total bleeding and major gastrointestinal system (GIS) bleeding among DOAC groups with them being higher for dabigatran 110 mg. Patients [17 (5.6%)] receiving apixaban 5 mg bid therapy had the lowest rates for bleeding events. Intracranial bleeding was observed in 6 (0.3%) patients (2 patients on dabigatran 110 mg bid, 2 on rivaroxaban 15 mg od, 1 on apixaban 2.5 mg bid, and 1 on apixaban 5 mg bid). No difference was observed for the rates of intracranial bleeding events among the DOAC groups (Table 5). A total of 140 (68.3%) patients required medical and surgical intervention, and 91 (44.4%) patients were hospitalized. The rates of temporary discontinuation and changes in anticoagulant therapy were 113 (55.1%) and 75 (36.6%) patients, respectively. A total of 12 (66.7%) patients were hospitalized among those receiving apixaban 2.65 mg bid. There was no significant difference among DOACs.

Sites of major bleeding

Our data showed that the most frequent location of major bleeding was the GIS in 17 (0.9%) patients, followed by intracranial bleeding in 6 (0.3%) patients. The other types of bleeding that were observed were hematuria in 4 (0.2%), epistaxis and bruising/ecchymosis in 3 (0.2%), and intramuscular in 1 (0.1%).

Sites of minor bleeding

In our study, the most frequent location of minor bleeding was the gingiva in 45 (2.5%) patients, followed by the GIS in 40 (2.2%) patients, and genitourinary system [hematuria in 23 (1.3%) patients]. Other types of minor bleeding were epistaxis in 21 (1.2%) patients and conjunctiva in 15 (0.8%) patients.

Management of bleeding

A total of 91 (44.4%) patients who experienced any type of bleeding were hospitalized. The medical or surgical therapies and interventions used for the management of bleeding were similar among the DOAC groups (Table 3). The anticoagulation therapy was changed for 75 (36.6%) patients, and the drug was temporarily discontinued in 113 (55.1%) patients; these rates were similar among the NOAC groups.

Discussion

Our study was the first multicentric 1-year prospective follow-up study in a large cohort of patients on DOAC treatment with the diagnosis of NVAF from different regions of Turkey. Because they were released into the market earlier, dabigatran 110 mg bid was the most prescribed DOAC, followed by rivaroxaban 20 mg od, and apixaban 5 mg bid. However, edoxaban was introduced to the DOAC market after this study and therefore was not included.

The demographic characteristics of our patients were similar to those of other studies (3-5, 7, 18-21). However, there was less CRF, higher GFR, and a higher rate of female patients regardless of the DOAC type. The average CHA2DS2-VASc score was similar to the RAMSES (9), AFTER (10), and NOAC-TR (11) studies. We also observed that low-dose DOAC was used in the treatment of patients with high CHA2DS2-VASc score, similar to a nationwide cohort study (19).

In this study, the total bleeding rate was 11.4%, higher than the first NOAC-TURK study findings of 217 (7.6%) patients. The

Anatol J Cardiol 2021; 25: 196-204
DOI:10.5152/AnatolJCardiol.2021.57635

Table 4. Multiple Cox regression analyses showing independent factors of bleeding

	Univariate		Multivariate	
Parameters	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Age (years)	1.016 (0.994–1.038)	0.158		
Sex	0.943 (0.674–1.32)	0.733		
GFR (mL/min/1.73 m^2)	0.996 (0.987–1.005)	0.374		
CHA2DS2-VASC score	0.885 (0.717–1.092)	0.254		
HAS-BLED score	1.353 (1.15–1.593)	<0.0001	1.321 (1.168–1.493)	<0.0001
ATRIA	1.042 (1.014–1.072)	0.004	1.041 (1.016–1.068)	0.001
ASA	1.516 (0.854–2.693)	0.155		
Clopidogrel	1.388 (0.336–5.742)	0.650		
Diabetes mellitus	0.835 (0.56–1.243)	0.374		
Hypertension	1.188 (0.773–1.825)	0.433		
Coronary artery disease	0.958 (0.648–1.415)	0.828		
Chronic heart failure	1.008 (0.685–1.482)	0.969		
Chronic renal failure	1.643 (0.996–2.711)	0.052		
Previous stroke, TIA	0.812 (0.484–1.364)	0.432		
Peripheral artery disease	2.026 (1.32–3.111)	<0.0001	2.083 (1.378–3.148)	<0.0001
Dabigatran 150 mg	1.107 (0.147–8.356)	0.922		0.023
Dabigatran 110 mg	0.974 (0.133–7.146)	0.979		
Rivaroxaban 20 mg	1.733 (0.234–12.859)	0.591	1.760 (1.228–2.524)	0.002
Rivaroxaban 15 mg	1.515 (0.204–11.232)	0.685		
Apixaban 5 mg	1.160 (0.151–8.943)	0.887		
Apixaban 2.5 mg	0.739 (0.096–5.685)	0.771		

GFR - glomerular filtration rate; ASA - acetylsalicylic acid; TIA - transient ischemic attack; HR - hazard ratio; CI - confidence interval

EORP-AF study (22) had similar results with our study as they reported the bleeding event rate at 8.4% and 11% for the first and second-year follow-up, respectively. In the literature, the annual rate of total bleeding and major bleeding in patients receiving DOAC treatment was reported to be 4.5%–5.4% and 2.1%–3.6%, respectively. For apixaban users, the rate of any bleeding event can rise to 18.1% per year (17).

In this study, the patients receiving DOAC had fewer bleeding events than those reported in the literature. This difference could be related to a shorter follow-up period (12+2 months). Furthermore, patients receiving lower dosage forms of DOACs had a higher incidence of bleeding events. This finding might be explained by impaired renal function (74.6±19.1 mL/min) and increased age (81.6±6 years). Patients taking apixaban (5 mg) bid had less major and non-major bleeding. The ARISTOTLE trial showed that minor bleeding was more common than major bleeding and occurred less frequently with apixaban than warfarin. In pilot trials, such as RE-LY and ARISTOTLE, minor bleeding was not the primary endpoint for safety (3, 5). Our data demonstrated that similar results for minor bleeding events but not for major bleeding events. Minor bleeding is clinically important because it is a common complication and often results in adverse consequences, including hospitalization and discontinuation or changes in effective anticoagulation that may lead to worse clinical outcomes. Helmert et al. (23) found in the Dresden study that the major bleeding rate was 2.8/100 patient-years and was significantly higher in patients receiving the 2.5 mg bid dose than those receiving the 5 mg bid dose (5.3 versus 2.2/100 patient-years) for apixaban. In our study, the bleeding events occurred more often with apixaban 2.5 mg bid than for apixaban 5 mg bid. However, the rate of bleeding was less than that of the Dresden study.

Furthermore, the population in the Dresden study was older (median age: 74 versus 72 years for apixaban 5 mg and 83 versus 81years for apixaban 2.5 mg), the follow-up period was more extended (median: 33 versus 12 months), and the number of patients with renal failure was less in our study for apixaban 2.5 mg (26.4% versus 14.7%) (23). In addition, Emren et al. (11) reported that approximately one-fifth of the patients receiving NOAC treatment had bleeding events. Despite the follow-up period of 3 months, major (4.9%) and minor (16%) bleeding was higher than our data. This difference might be related to the lower mean HAS-BLED score of the patients who participated in our study (2±1.2 versus 3±1, respectively).

The major and minor clinically relevant bleeding has been shown to occur in 1.9% and 12.9% patients, respectively, in the

Table 5. Sites and management of bleeding

Sites of minor bleeding	Dabigatran 150 mg (n=273)	Dabigatran 110 mg (n=409)	Rivaroxaban 20 mg (n=385)	Rivaroxaban 15 mg (n=276)	Apixaban 5 mg (n=308)	Apixaban 2.5 mg (n=156)	Total (n=1.807)	*P*
GIS, n (%)	5 (1.8)	12 (2.9)	8 (2.1)	9 (3.3)	4 (1.3)	2 (1.3)	40 (2.2)	0.320
Epistaxis, n (%)	6 (2.2)	7 (1.7)	2 (0.5)	2 (0.7)	2 (0.6)	2 (1.3)	21 (1.2)	0.495
Hematuria, n (%)	2 (0.7)	3 (0.7)	5 (1.3)	2 (0.7)	5 (1.6)	6 (3.8)	23 (1.3)	0.700
Hemoptysis, n (%)	1 (0.4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.1)	0.533
Bruising/ecchymosis, n (%)	1 (0.4)	0 (0)	1 (0.3)	0 (0)	0 (0)	0 (0)	2 (0.1)	0.896
Urinary system/vaginal, n (%)	0 (0)	1 (0.2)	1 (0.3)	0 (0)	1 (0.3)	0 (0)	3 (0.2)	0.999
Intramuscular, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.6)	1 (0.1)	0.900
Conjunctival, n (%)	2 (0.7)	3 (0.7)	8 (2.1)	0 (0)	1 (0.3)	1 (0.6)	15 (0.8)	0.081
Intra-articular, n (%)	0 (0)	2 (0.5)	1 (0.3)	1 (0.4)	0 (0)	0 (0)	4 (0.2)	0.449
Retroperitoneal, n (%)	1 (0.4)	2 (0.5)	1 (0.3)	2 (0.7)	0 (0)	0 (0)	6 (0.3)	0.881
Gingival bleeding, n (%)	12 (4.4)	11 (2.7)	13 (3.4)	9 (3.3)	0 (0)	0 (0)	45 (2.5)	0.744
Sites of major bleeding								
GIS, n (%)	1 (0.4)	10 (2.4)	2 (0.5)	1 (0.4)	1 (0.3)	2 (1.3)	17 (0.9)	0.289
Epistaxis, n (%)	0 (0)	0 (0)	1 (0.3)	1 (0.4)	1 (0.3)	0 (0)	3 (0.2)	0.990
Hematuria, n (%)	0 (0)	0 (0)	0 (0)	3 (1.1)	1 (0.3)	0 (0)	4 (0.2)	0.970
Hemoptysis, n (%)	0 (0)	0 (0)	0 (0)	2 (0.7)	0 (0)	0 (0)	2 (0.1)	0.977
Bruising/ecchymosis, n (%)	1 (0.4)	0 (0)	0 (0)	1 (0.4)	0 (0)	1 (0.6)	3 (0.2)	0.999
Urinary system/vaginal, n (%)	0 (0)	1 (0.2)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.1)	0.982
Intramuscular, n (%)	0 (0)	0 (0)	1 (0.3)	0 (0)	0 (0)	0 (0)	1 (0.1)	0.989
Intracranial, n (%)	0 (0)	2 (0.5)	0 (0)	2 (0.7)	1 (0.3)	1 (0.6)	6 (0.3)	0.9920
Management of bleeding								
Medical or surgical intervention	18 (56.3)	36 (63.2)	32 (69.6)	27 (77.1)	12 (70.6)	15 (83.3)	140 (68.3)	0.300
Hospitalization	11 (34.4)	26 (45.6)	15 (32.6)	18 (51.4)	9 (52.9)	12 (66.7)	91 (44.4)	0.120
Temporary discontinuation	14 (43.8)	26 (45.6)	29 (63)	21 (60)	10 (58.8)	14 (77.8)	113 (55.1)	0.119
Change in antithrombotic therapy	13 (40.6)	22 (38.6)	14 (30.4)	11 (31.4)	9 (52.9)	6 (33.3)	75 (36.6)	0.634

Categorical variables were compared by the χ^2 test. GIS - gastrointestinal system

rivaroxaban study; the results were in line with our study (24). The major bleeding and total bleeding rates with dabigatran 110 mg bid were 2.71% and 14.62%, respectively, per year in the RE-LY study (3). Both these rates have been reported to increase to 3.11%and 16.42%, respectively, per year with dabigatran 150 mg bid. However, in our study, patients receiving dabigatran 110 mg bid (13.9%) had more total bleeding events than those who received dabigatran 150 mg bid (11.7%). In addition, patients in our study who received dabigatran 150 mg bid were younger (median age: 68.7 versus 76.5 years), had a lower HAS-BLED score (1.9 versus 2.2), and better renal functions (3.3% versus 10.3%). In addition, there was no intracranial bleeding with dabigatran 150 mg, which was not observed in the Spanish cohort either (25).

In a previous study, rivaroxaban 15 mg was associated with higher major bleeding events than rivaroxaban 20 mg (2.2% and 1.5%, respectively) (26). Furthermore, Huang et al. (27) have also reported that rivaroxaban 15 mg was related to a higher number of intracranial bleeding and GIS bleeding events than rivaroxaban 20 mg. Therefore, this current study showed that a reduced dose of DOACs was associated with higher bleeding events. Our data are similar with previous studies (22, 26, 27). This paradox may be associated with group variation. In this study, the treatment dosage might have been determined by physicians on the basis of their judgment in the clinical setting. Hence, patients in the high dose DOACs group tended to be less fragile and had a lower risk of bleeding as indicated by lower HAS-BLED scores. However, patients taking high doses were older, more fragile, had poor renal function, and higher CHA2DS2-VASc, HAS-BLED, and ATRIA scores.

In this study, we showed that bleeding events were lower than those in some previous pilot studies. This difference might

Anatol J Cardiol 2021; 25: 196-204
DOI:10.5152/AnatolJCardiol.2021.57635

be explained by the lower HAS-BLED score, younger age, and higher GFR (3-5). During our study, the physicians likely had concerns about bleeding in patients treated by DOAC; therefore, they may have chosen patients with lower HAS-BLED scores and a lower ratio of patients with renal impairment for treatment. However, our results are similar to those of the Spanish cohort that investigated the effectiveness and safety of treatment of DOAC in daily practice (25).

In this study, 15 (66.7%) patients taking apixaban (2.5 mg) bid were hospitalized. This could be explained by the fragility of these patients owing to age and high morbidity. In the ARISTOTLE study, patients presenting with minor bleeding were slightly more likely to require medical or surgical consultations (78.8%) compared with those treated with warfarin (70.1%). This study had similar results; 15 (83.3%) patients on apixaban (2.5 mg) required medical or surgical consultation. However, hospitalizations were higher in our study than in previous studies (66.7% versus 12.9%) (28). The mean age of patients on apixaban in the ARISTOTLE study was 70 years, whereas in this study, it was 81.6 years. The high rate of hospitalization might be explained by the older and more fragile patient population. Furthermore, 118 patients on apixaban (2.5 mg) were hospitalized in the ARISTOTLE study; however, only 12 patients were hospitalized in this study because our number of patients on apixaban (2.5 mg) and other DOACs were less than those in the previous pilot studies (28). This finding could also be a result of concern about the use of DOAC and a lack of knowledge about the options for the management of DOAC-related bleeding. Bleeding management and outcomes were evaluated and compared with those of the RE-LY study. The number of medical or surgical interventions, hospitalizations, temporary discontinuities, and change in antithrombotic therapy was higher in this study than in previous studies. This difference could be explained by the easy access to healthcare and health policy of the region as well as the geographic properties and difficulties in transportation. This study was a real-life follow-up study and consisted of unselected patients.

We demonstrated that a total bleeding event occurred most often in the GIS tract (GIST) and was more frequent with rivaroxaban and dabigatran than apixaban. This was followed by bleeding in the urinary tract and skin without any significant statistical difference. However, major bleeding in the GIST was the most frequent in patients [10 (2.4%)] receiving dabigatran 110 mg bid. In the RE-LY study, dabigatran 150 mg bid increased the relative risk of major GIST bleeding. However, patients receiving dabigatran 110 mg bid had lower GIST bleeding. Dabigatran was the first DOAC in Turkey, and the side effect of GIST is well known. Therefore, dabigatran 110 mg bid might be given to patients with the disease and symptoms of GIST. Patients receiving dabigatran 150 mg bid also had a lower bleeding risk score, age, and renal impairment, although a recent systematic review and meta-analysis have demonstrated that there was no difference between the types of DOAC (29). The Spanish cohort (25) had similar results as our study, and other previous studies also have described similar bleeding locations.

Although minor bleeding from the gingival appeared to be more common with DOAC in our study, we could not obtain sufficient information on gingival bleeding with DOACs. However, we believe it could be related to periodontal health.

The main objective of this study was to analyze the safety of DOAC in clinical practice in Turkey. It has shown fewer bleeding events than in previous pilot studies, which might be explained by lower HAS-BLED (2.0±1.2) and ATRIA (4.8±4.3) scores. There was also a lower CRF [167 (9.2%)] count and a shorter follow-up period.

We determined the risk factors using multiple Cox regression analyses for bleeding; rivaroxaban 20 mg od, PAD, ATRIA, and HAS-BLED were the independent indicators of bleeding. PAD was associated with bleeding in this study. The EUCLID study showed that the bleeding events of patients with PAD treated with antiplatelet agents were higher than those without PAD (30). Moreover, the first step of NOAC-TURK study demonstrated higher bleeding events in patients with PAD (8). Overall, these results might be associated with patients with PAD who are older and have more severe disease. Future studies of patients with PAD should investigate this association in detail.

In this study, we found that rivaroxaban 20 mg was an independent risk factor for bleeding (HR=1.760, 95% CI: 1.228–2.524, p=0.002). These data are consistent with the results of the previous real-life data that showed that rivaroxaban 20 mg is associated with a higher bleeding risk than other DOACs (31, 32). Furthermore, in the ROCKET-AF trial, the rates of bleeding events were similar for rivaroxaban and warfarin (4). The Spanish cohort also demonstrated that rates of major bleeding were slightly higher with rivaroxaban.

Study limitations

Unfortunately, we could not reach some of the participants from the first step of the NOAC-TURK study. The bias introduced could not be completely avoided. The DOAC medication prescribed was dependent on the time the drug was introduced into the market and its reimbursement; thus, edoxaban could not be included in the study. In this study, we could not obtain the data about the use of nonsteroidal anti-inflammatory drugs because our participants may have taken them without a prescription. Therefore, this might have affected the HAS-BLED score. The possible difference among the types of DOACs in the occurrence of intracranial bleeding could not be clearly elucidated because of the low number of intracranial bleeding events. Finally, we could not collect the data on the management of bleeding because of the insufficiency of the national health record system. The discontinuation was reported as temporary owing to not obtaining the exact number of permanent discontinuation from all centers.

Conclusion

This prospective study looked at a large cohort of patients with NVAF and reflects the results obtained using DOACs in a clinical practice in Turkey. The major and intracranial bleeding

were similar for different DOACs. Rivaroxaban 20 mg od was an independent indicator of bleeding, and reduced dosage of DOACs is associated with higher bleeding rates. The GIST and gingiva were the most common sites for major and minor bleeding, respectively.

Conflict of interest: None declared.

Peer-review: Externally peer-reviewed.

Author contributions: Concept - Ö.G., S.A., M.Ş., S.P.; Design - Ö.G., S.A., M.Ş., S.P.; Supervision - Ö.G., H.A.Ç., L.A., U.C., M.Ş., S.P.; Fundings - F.B., Ü.Y.S., U.C.; Materials - H.A.Ç., A.Y., F.B., Ü.Y.S., U.C.; Data collection &/or processing - Ö.G., S.A., S.Ü., H.A.Ç., L.A., A.Y., F.B., Ü.Y.S., U.C.; Analysis &/or interpretation - Ö.G., S.Ü., L.A., A.Y.; Literature search - Ö.G., S.A., S.Ü., S.P.; Writing - Ö.G., S.Ü.; Critical review - Ö.G., S.Ü., H.A.Ç., L.A., A.Y., F.B., Ü.Y.S., U.C.

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