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Real-World Data on the Incidence of Stroke, Myocardial Infarction, and Mortality Among Nonvalvular Atrial Fibrillation Patients in Türkiye: New Oral Anticoagulants-TURKey Study

ABSTRACT

Background: Atrial fibrillation (AF) is strongly associated with an increased risk of ischemic events. Anticoagulation focuses on reducing the risk of embolism. Guideline recommended CHA_2DS_2-VASc scoring system is most widely used; however, different scoring systems do exist. Thus, we sought to assess the impact of anticoagulant treatment and different scoring systems on the development of stroke, myocardial infarction, and all-cause mortality in patients with nonvalvular AF.

Methods: The present study was designed as a prospective cohort study. The enrollment of the patients was conducted between August 1, 2015, and January 1, 2016. The follow-up period was defined as the time from enrollment to the end of April 1, 2017, which also provided at least 12 months of prospective follow-up for each patient.

Results: A total of 1807 patients with AF were enrolled. During the follow-up, 2.7% (48) of patients had stroke, 0.8% (14) had myocardial infarction, and 7.5% (136) died. The anticoagulation and risk factors in AF (ATRIA) score had a better accuracy for the prediction of stroke compared to other scoring systems (0.729, 95% CI, 0.708-0.750, $P < .05$). Patients under low-dose rivaroxaban treatment had significantly worse survival (logrank $P < .001$). Age, CHA_2DS_2-VASc score, R_2CHADS_2 score, ATRIA score, chronic heart failure, prior stroke, and being under low-dose rivaroxaban treatment were independent predictors of clinical endpoint ($P < .001$).

Conclusion: Low-dose rivaroxaban treatment was independently and strongly associated with the combined clinical endpoint. Furthermore, the ATRIA score proved to be a stronger predictor of stroke in the Turkish population.

Keywords: Anticoagulant agents, atrial fibrillation, death, ischemic stroke, myocardial infarction

INTRODUCTION

Atrial fibrillation (AF) is the most common sustained arrhythmia diagnosed in clinical practice, particularly in the elderly.[1] It is associated with an increased risk of ischemic stroke, mortality, heart failure, vascular dementia, and reduced cognitive function. Treatment of AF should focus on restoring sinus rhythm, controlling heart rate, and reducing the risk of embolism by anticoagulant therapy.[1,2] Guidelines on the treatment of AF have established indications depending on the CHA_2DS_2-VASc scoring system, which assesses the risk of ischemic stroke due to AF.[1,3] However, there are several scoring systems suggested for predicting ischemic stroke risk in patients with AF.[4,5] Frequent changes and discontinuation of medications usually hamper the efficacy of anticoagulation treatment. On the other hand, medication adherence increased considerably with the introduction of direct oral anticoagulants. Although several randomized studies have been performed to prove the superiority and noninferiority of non-vitamin K antagonist oral anticoagulants (NOACs) in comparison to vitamin K antagonists, real-world data can show different findings in daily practice.[6-9] Therefore, we sought to assess the impact of anticoagulant treatment and the prediction capacity of different scoring systems on the development of stroke, myocardial infarction,

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and all-cause mortality in patients with nonvalvular AF in at least 12 months of follow-up.

METHODS

The study protocol has been previously published.[10,11] In brief, the present project was designed as a prospective cohort study investigating the composite of clinical endpoints including stroke, myocardial infarction, and all-cause mortality in patients receiving NOACs in at least 12 months' follow-up. The patient population was a subgroup of New Oral Anticoagulants-TURKey (NOAC-TURK) study registry who was receiving NOAC treatment with an indication of nonvalvular AF. The enrollment of the patients was conducted between August 1, 2015, and January 1, 2016. The follow-up period was defined as the time from enrollment to the end of April 1, 2017, which also provided at least 12 months prospective follow-up for each patient. A total of 1807 subjects from 9 centers were included in prospective analysis.

The main inclusion criteria were being older than 18 years, having the ability to give consent under treatment of NOAC with the diagnosis of nonvalvular AF. The follow-up of the patients was performed in outpatient's clinics, by face-to-face interview, or via telephone.

Patient information regarding demographic, clinical, and laboratory characteristics of study participants was obtained via the NOAC-TURK survey database. New clinical and laboratory findings were added where available. Medical records of composite endpoint were obtained from participating centers via electronic file transfers. Transient ischemic attack (TIA) is defined as a transient episode of neurological dysfunction resulting from focal brain, spinal cord, or retinal ischemia, wherein infarction does not occur. On the other hand, stroke is defined as an infarction of central nervous system tissue.[12] Acute myocardial infarction is defined as the presence of evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischemia, which can be confirmed by detecting a rise and/or fall of cardiac biomarker values with at least 1 value above the 99th percentile upper reference limit by also encompassing the presence of symptoms and findings of myocardial ischemia with electrocardiogram or imaging methods.[13] Mortality data were obtained from electronic health records of participating centers.

Ischemic risk scores including CHA_2DS_2-VASc, R_2CHADS_2, HAS–BLED, and anticoagulation and risk factors in AF (ATRIA) scores of patients were recalculated. Glomerular filtration rate (GFR) was calculated by using modification of diet in renal disease formula.[14]

The study was approved by ethical commission of the Ethics Committee of Haydarpaşa Numune Training and Research Hospital (HNEAH-KAEK 2015/KK/60), and all subjects gave written informed consent prior to inclusion.

Statistical Analysis

Continuous variables are presented as mean ± standard deviation, and categorical data are presented as percentages or frequencies. Continuous variables were examined by Kolmogorov–Smirnov test to check for normality of distribution. Baseline characteristics were compared among groups using the Student *t*-test or 1-way analysis of variance test. Categorical variables were compared using the χ^2 test. The study population was divided into 2 groups according to the reaching clinical endpoint. Baseline characteristics were compared between the groups using the student *t*-test or the χ2 test. Receiver operating characteristic (ROC) curves were calculated to evaluate the prediction of the clinical endpoint within follow-up period. Comparison between the area under the curve (AUC) values was performed by using De Long test[15] (Medcalc Software, Mariakerke, Belgium). The patient population was further categorized based on used NOAC type. Patients were grouped depending on ATRIA[4] and HAS–BLED[16] scores as follows; ATRIA score (0-5 points): low risk of stroke (<1%), ATRIA score (6 points): intermediate risk of stroke (1%-<2%), ATRIA score (>6 points): high risk of stroke (≥2%), HAS–BLED score (≤1 points): relatively low risk of bleeding, HAS–BLED score (2 points): moderate risk of bleeding, HAS–BLED score (<2, ≤5 points): high risk of bleeding, HAS–BLED score (>5 points): very high risk of bleeding. Kaplan–Meier curves were constructed to compare survival between groups, and considering the date of the study inclusion, the logrank test was used to determine significance. Pairwise comparisons among groups under treatment involving different types of NOACs and various dosages are conducted to assess the specific effects and differentiations within this therapeutic context. This analytical approach provided a detailed examination of the comparative outcomes and impacts of distinct anticoagulant agents and their respective dosages on the relevant clinical endpoint. The *P*-values of pairwise comparisons are obtained by using logrank (Mantel–Cox) test. Significant determinants of clinical endpoint were also assessed with the Cox proportional hazard model with forward stepwise likehood ratio. Gender, type of NOAC, and having comorbidities were encoded as categorical variables, and the rest were encoded as continuous variables and analyzed in a multivariate model against the endpoint. The significance level to remain in the multivariate model was 0.1. A 2-tailed *P*-value of ≤.05 was considered statistically significant. All data were analyzed using Statistical Package for the Social Sciences Statistics version 23.0 (IBM, Armonk, NY, USA).

HIGHLIGHTS

- Low-dose rivaroxaban treatment was associated with worse survival.
- Age, low-dose rivaroxaban treatment, CHA_2DS_2-VASc score, R_2CHADS_2 score, and anticoagulation and risk factors in atrial fibrillation (ATRIA) score were independently associated with worse clinical outcome.
- The ATRIA risk score is a stronger predictor of stroke in the Turkish population.

RESULTS

Study Population

A total of 1807 nonvalvular AF patients with follow up data were enrolled. Basal characteristics of the study population are presented in Table 1. Supplementary Table 1 presents

Table 1. Baseline Characteristics of Study Patients

Characteristic	Total (n = 1807)	Group Without Clinical Endpoint (n = 1621)	Group with Clinical Endpoint (n = 186)	*P*
Age (years)	73.6 ± 10.2	73.1 ± 10.4	77.5 ± 9.3	<.001
Age ≥ 85	318 (17.6)	306 (18.9)	12 (6.5)	<.001
Age 75-84	564 (31.2)	508 (31.3)	56 (30.1)	
Age 65-74	694 (38.4)	619 (38.2)	75 (40.3)	
Age < 65	231 (12.8)	188 (11.6)	43 (23.1)	
Female (n, (%))	1106 (61.4)	994 (61.3)	112 (60.2)	.751
Baseline Comorbidities				
Previous stroke, TIA (n, (%))	213 (11.8)	173 (10.7)	40 (21.5)	<.001
Diabetes mellitus (n, (%)	382 (21.1)	344 (21.2)	38 (20.4)	.850
Hyperlipidemia (n, (%))	822 (45.5)	752 (46.4)	70 (37.6)	.024
Hypertension (n, (%))	1558 (86.2)	1398 (86.2)	160 (86)	.911
Coronary artery disease (n, (%))	483 (26.7)	436 (26.9)	47 (25.3)	.663
Chronic heart failure (n, (%))	522 (28.9)	449 (27.7)	73 (39.2)	.002
Chronic renal failure (n, (%))	167 (9.2)	139 (8.6)	28 (15.1)	.007
Peripheral artery disease (n, (%))	151 (8.4)	142 (8.8)	9 (4.8)	.069
GFR (mL/min/1.73 m^2)	78.3 ± 21.3	78.7 ± 21.2	74.1 ± 21.2	.008
GFR Groups				
<30	16 (0.9)	8 (0.5)	8 (4.3)	<.001
30-60	329 (18.2)	280 (17.3)	49 (26.3)	
60-90	929 (51.4)	842 (51.9)	87 (46.8)	
>90	533 (29.5)	491 (30.3)	42 (22.6)	
CHA_2DS_2-VASc Score				
Mean	3.9 ± 1.5	3.8 ± 1.5	4.3 ± 1.5	<.001
CHA_2DS_2-VASc score (n, (%))				.001
0	13 (0.7)	13 (0.8)	0 (0)	
1	100 (5.5)	93 (5.7)	7 (3.8)	
2	274 (15.2)	256 (15.8)	18 (9.7)	
3	455 (25.2)	421 (26)	34 (18.3)	
4	520 (28.8)	455 (28.1)	65 (34.9)	
5	278 (15.4)	245 (15.1)	33 (17.7)	
6	112 (6.2)	96 (5.9)	16 (8.6)	
7	37 (2)	27 (1.7)	10 (5.4)	
8	17 (0.9)	14 (0.9)	3 (1.6)	
9	1 (0.1)	1 (0.1)	0 (0)	
10	13 (0.7)	13 (0.8)	0 (0)	
R_2CHADS Score				
Mean	2.5 ± 1.5	2.4 ± 1.4	3.2 ± 1.6	<.001
R_2CHADS score (n, (%))				<.001
0	74 (4.1)	72 (4.4)	2 (1.1)	
1	392 (21.7)	364 (22.5)	28 (15.1)	
2	599 (33.1)	549 (33.9)	50 (26.9)	
3	319 (17.7)	287 (17.7)	32 (17.2)	
4	240 (13.3)	205 (12.6)	35 (18.8)	
5	113 (6.3)	92 (5.7)	21 (11.3)	
6	48 (2.7)	38 (2.3)	10 (5.4)	
7	19 (1.1)	11 (0.7)	8 (4.3)	
8	3 (0.2)	3 (0.2)	0 (0)	

(*Continued*)

Table 1. Baseline Characteristics of Study Patients (*Continued*)

Characteristic	Total (n = 1807)	Group Without Clinical Endpoint (n = 1621)	Group with Clinical Endpoint (n = 186)	*P*
HAS–BLED Score				
Mean	2 ± 1.2	2 ± 1.1	2.3 ± 1.2	<.001
HAS–BLED score groups (n, (%))				
0-1 Low	570 (60.4)	530 (32.7)	40 (21.5)	<.001
2 Moderate	679 (37.6)	616 (38)	63 (33.9)	
3-5 High bleeding risk	554 (30.7)	471 (29.1)	83 (44.6)	
>5* Very high	4 (0.2)	4 (0.2)	0	
ATRIA Score				
Mean	6.1 ± 2.5	6 ± 2.5	7.5 ± 2.4	<.001
ATRIA score (n, (%))				<.001
Low risk of stroke (<1%): 0-5 points	660 (36.5)	627 (38.7)	33 (17.7)	
Intermediate risk of stroke (1%-<2%): 6 points	251 (13.9)	233 (14.4)	18 (9.7)	
High risk of stroke (≥2%): > 6 points	896 (49.6)	761 (46.9)	135 (72.6)	

Student - *t* test was used for continuous variables. Categorical variables were compared by the χ^2 test.
ATRIA, anticoagulation and risk factors in atrial fibrillation; GFR, glomerular filtration rate; TIA, transient ischemic attack.

basal characteristics depending on the type of NOAC used and meeting clinical endpoint.

A total of 186 (10.3%) patients met the clinical endpoint (group with clinical endpoint), while 1621 (89.7%) patients did not meet the clinical endpoint (group without clinical endpoint). There was no difference in gender between groups depending on whether they met the clinical endpoint. However, patients with clinical endpoint were older and had significantly increased comorbidities of previous stroke, chronic renal disease, chronic heart failure, and worse GFR. Moreover, the CHA_2DS_2-VASc, R_2CHADS_2, HAS–BLED, and ATRIA scores were significantly higher for the patients who met clinical endpoint.

Predictors of Clinical Outcome

During follow-up, 48 (2.7%) patients had stroke, and 14 (0.8%) patients had myocardial infarction. A total of 136 (7.5%) patients died. The cause of death could not be determined in 109 patients. The number of deaths due to stroke, myocardial infarction, and bleeding were 11, 4, and 12, respectively. Detailed information on frequencies of composites of endpoint is given in Table 2. The mean follow-up time was 18.2 ± 3.1 months. The AUC of the ROC analysis for stroke prediction by ATRIA score (0.729; 95% CI, 0.708-0.750) was superior to CHA_2DS_2-VASc [0.615; 95% CI, 0.592-0.638, (vs. ATRIA score P = .038)] and R_2CHADS_2 [0.613; 95% CI, 0.590-0.635, (vs. ATRIA score P = .032)] scores (Figure 1). The ATRIA score demonstrated a good accuracy for the prediction of stroke,

Table 2. Frequencies of Endpoint Composites Depending on the Type of Non-vitamin K Antagonist Oral Anticoagulants

	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)
Stroke (n, (%))	4 (1.5)	11 (2.7)	5 (1.3)	10 (3.6)	4 (1.3)	3 (1.9)
Death (n, (%))	10 (3.7)	24 (5.9)	23 (6)	27 (9.8)	15 (4.9)	10 (6.4)
Major bleeding causing death (n, (%))	2 (0.7)	4 (1)	1 (0.3)	3 (1.1)	1 (0.3)	1 (0.6)
Stroke causing death (n, (%))	0 (0)	2 (0.5)	0 (0)	7 (2.5)	2 (0.6)	0 (0)
Myocardial infarction causing death (n, (%))	1 (0.4)	1 (0.2)	0 (0)	2 (0.7)	0 (0)	0 (0)
Myocardial infarction (n, (%))	2 (0.7)	2 (0.5)	1 (0.3)	3 (1.1)	1 (0.3)	1 (0.6)
Worsening heart failure (n, (%))	(0)	1 (0.2)	(0)	1 (0.4)	(0)	1 (0.6)
Endpoint (n, (%))	19 (7)	45 (11)	30 (7.8)	53 (19.2)	23 (7.5)	16 (10.3)

Bid, twice a day; od, once a day.

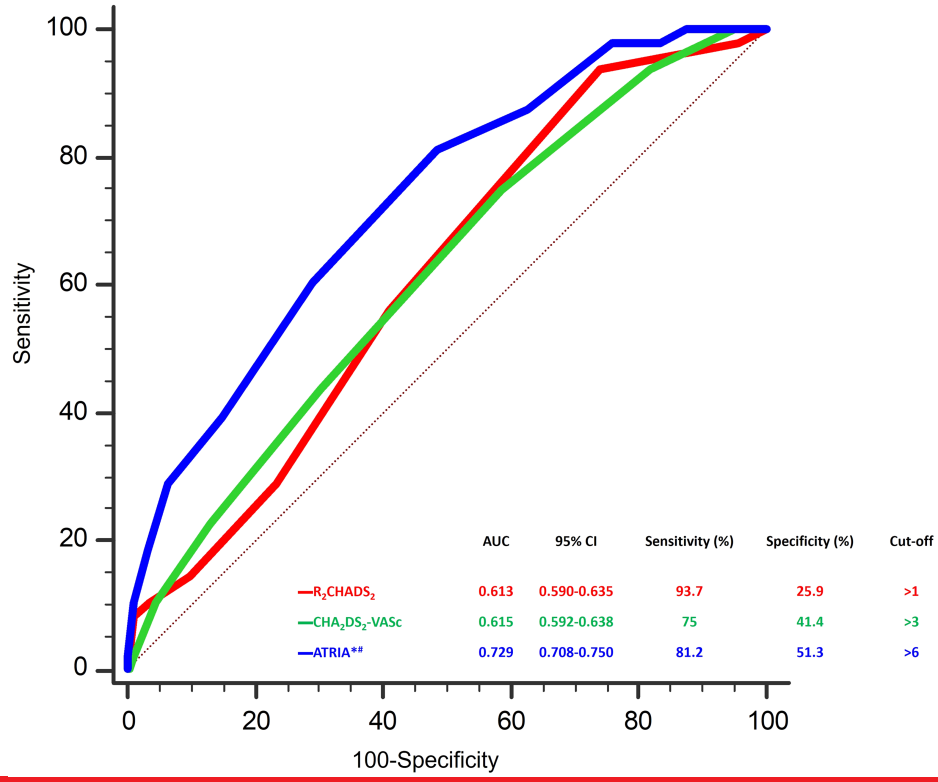


Figure 1. Receiver operating characteristic curves for CHA_2DS_2-VASc, R_2CHADS_2, and ATRIA scores showing the ability of each parameter to predict stroke. The respective area under the curve and 95% CIs for each parameter are listed in tables. * significant difference for CHA_2DS_2-VASc score and # indicates significant difference from R_2CHADS_2 score ($P < .05$). ATRIA, anticoagulation and risk factors in atrial fibrillation; AUC, area under the curve.

with a sensitivity of 81.2% and specificity of 51.3% for a criterion >6 for Turkish population (Figure 1).

Kaplan–Meier survival curves when patients were divided according to type of NOAC showed that patients under low-dose rivaroxaban treatment had significantly worse survival (Figure 2, logrank $P < .001$).

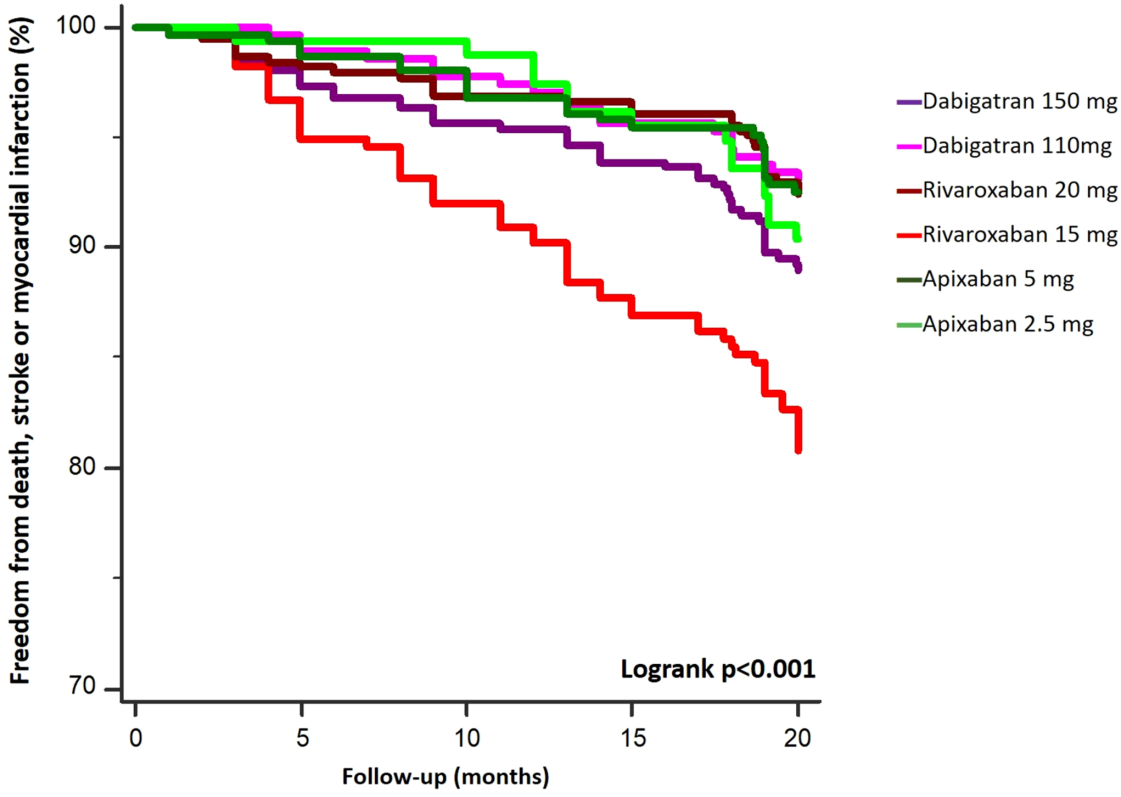
The results of the Cox regression model for the prediction of clinical endpoint are shown in Table 3. In the multivariate model, age, CHA_2DS_2-VASc score (hazard ratio (HR) = 1.255, CI: 1.055-1.5, $P = .011$), R_2CHADS_2 score (HR = 1.17, CI: 1.002-1.368, $P = .047$), ATRIA score (HR = 1.136, CI: 1.092-1.18, $P < .001$), having chronic heart failure (HR = 1.513, CI: 1.065-2.148, $P = .021$), prior stroke/TIA (HR = 1.769, CI: 1.126-2.777, $P = .013$), peripheral artery disease (HR = 2.549, CI: 1.244-5.221, $P = .011$), and being under low-dose rivaroxaban treatment (HR = 1.808, CI: 1.023-3.197, $P = .042$) were found as independent predictors of clinical endpoint (Table 3, Figure 3).

DISCUSSION

This study is the first of its kind to follow a large cohort of non-valvular AF patients treated with NOAC for at least 1 year, conducted in multiple centers across Türkiye. We showed that being under low-dose rivaroxaban treatment was independently and strongly associated with the composite clinical endpoint. Furthermore, the ATRIA score proved to be a stronger predictor of stroke than the CHA_2DS_2-VASc score, which is the risk scoring system recommended by guidelines to assess the development of ischemic stroke.

Dabigatran 110 mg bid (twice a day) was the most prescribed NOAC, followed by rivaroxaban 20 mg bid, and apixaban 5 mg bid, probably due to their earlier introduction. However, edoxaban was not included in our study as it was not yet available at the time of study initiation. Baseline characteristics and their impact on outcomes have been previously published and discussed.[10] In summary, we found that the demographic characteristics of the patients in the study were similar to other studies, but the rates of chronic renal failure were lower, GFR was higher, and the proportion of female patients was higher. Patients with high CHA_2DS_2-VASc scores were generally prescribed low-dose NOACs, which is consistent with the literature.[6,17-19] However, there were differences in the characteristics of patients receiving different NOACs; some were younger and had lower CHA_2DS_2-VASc scores and less renal impairment, while others had higher CHA_2DS_2-VASc scores, HAS–BLED scores, and worse renal function. These differences may be due to older age and lower GFR, which may have influenced physicians' choice of treatment.

There are currently few publications in the literature comparing NAOCs with each other.[20-22] Randomized controlled trials usually include a narrow and unrepresentative patient population with specific characteristics, whereas real-life data have a wider range of baseline characteristics.



Number at risk					
Dabigatran 150 mg	273	270	267	261	0
Dabigatran 110mg	409	398	391	384	0
Rivaroxaban 20 mg	385	378	373	370	0
Rivaroxaban 15 mg	276	262	254	240	0
Apixaban 5 mg	308	304	298	294	0
Apixaban 2.5 mg	156	155	154	149	0

***p*-values of pairwise comparisons among groups under treatment of different types of non-vitamin K antagonist oral anticoagulants and dosages**

	Dabigatran 150 mg	Dabigatran 110mg	Rivaroxaban 20 mg	Rivaroxaban 15 mg	Apixaban 5 mg	Apixaban 2.5 mg
Dabigatran 150 mg		0.075	0.697	<0.001	0.819	0.245
Dabigatran 110mg	0.075		0.116	0.003	0.106	0.753
Rivaroxaban 20 mg	0.697	0.116		<0.001	0.871	0.365
Rivaroxaban 15 mg	<0.001	<0.001	<0.001		<0.001	0.013
Apixaban 5 mg	0.819	0.106	0.871	<0.001		0.322
Apixaban 2.5 mg	0.245	0.753	0.365	0.013	0.322	

Figure 2. Kaplan–Meier survival curves for freedom from composite of clinical endpoint including stroke, myocardial infarction, and all-cause mortality according to the type and dosage of new oral anticoagulant agent. Number at risk table is presented below. *P*-values of pairwise comparisons among groups under treatment involving different types of non-vitamin K antagonist oral anticoagulants and various dosages are also presented. Notably, the observed significance primarily emanates from the low-dose rivaroxaban treatment.

Table 3. Univariate and Multivariate Predictors of Clinical Endpoint Among Patients Using Cox Regression Analysis

	Univariable			Multivariable		
Parameter	**Hazard Ratio**	***P***	**(95% CI)**	**Hazard Ratio**	***P***	**(95% CI)**
Age (years)	1.048	<.001	1.031-1.066	1.034	.001	1.013-1.055
Gender (m)	1.142	.372	0.853-1.528			
GFR (mL/min/1.73 m^2)	0.990	.008	0.983-0.997			
CHA_2DS_2-VASc score	1.309	<.001	1.191-1.439	1.255	.011	1.055-1.5
R_2CHADS_2 score	1.427	<.001	1.308-1.558	1.17	.047	1.002-1.368
ATRIA score	1.163	<.001	1.125-1.203	1.136	<.001	1.092-1.18
Diabetes mellitus	1.050	.788	0.735-1.500			
Hypertension	1.029	.892	0.680-1.557			
Coronary artery disease	1.086	.626	0.780-1.511			
Chronic heart failure	1.646	.001	1.226-2.210	1.513	.021	1.065-2.148
Chronic renal failure	1.831	.003	1.225-2.736			
Previous stroke	2.169	<.001	1.529-3.078	1.769	.013	1.126-2.777
Peripheral artery disease	1.830	.077	0.937-3.575	2.549	.011	1.244-5.221
NOAC type		<.001			.006	
Apixaban 2.5 mg bid (reference)						
Dabigatran 150 mg bid	0.676	.249	0.348-1.315	0.736	.403	0.358-1.512
Dabigatran 110 mg bid	1.096	.754	0.619-1.938	0.998	.994	0.55-1.809
Rivaroxaban 20 mg od	0.759	.372	0.414-1.392	0.939	.851	0.489-1.803
Rivaroxaban 15 mg od	2.004	.015	1.146-3.506	1.808	.042	1.023-3.197
Apixaban 5 mg bid	0.726	.326	0.384-1.375	0.874	.693	0.447-1.707

Gender, diabetes mellitus, hypertension, coronary artery disease, chronic heart failure, chronic renal failure, previous stroke/transient ischemic attack, peripheral artery disease, and NOAC type were encoded as categorical variables, and the rest were encoded as continuous variables. Apixaban 2.5 mg bid was chosen as the reference group among NOAC subgroups.
ATRIA, anticoagulation and risk factors in atrial fibrillation; bid, twice a day; GFR, glomerular filtration rate; NOAC, new oral anticoagulant agents; od, once a day.

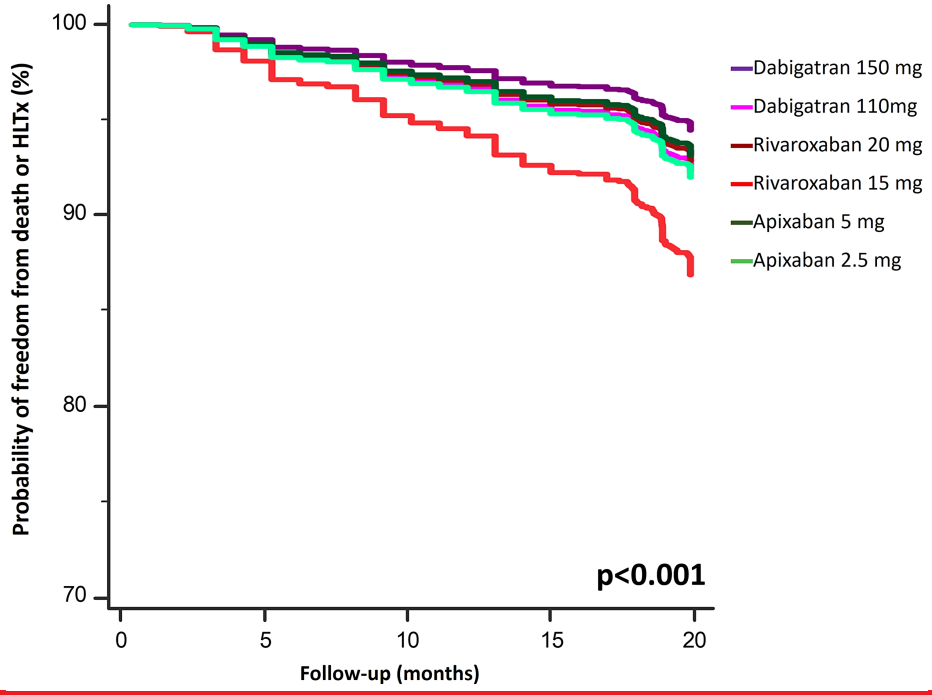


Figure 3. Probability of freedom from composite of clinical endpoints including stroke, myocardial infarction, and all-cause mortality from multivariate Cox regression analysis.

The prevalence of low-dose NOAC use is also more frequently observed in real-life data.[6,7,9,17,23] Similar to the findings of our study, low-dose NOAC users are generally older than standard-dose NOAC users, which may explain the higher mortality risk for low-dose NOACs. In our study, the low-dose NOAC group had older patients with lower GFR, higher stroke risk scores and HAS-BLED scores than the standard-dose NOAC group. In addition, there were differences in the medical history of the patients, such as hypertension, diabetes, heart failure, vascular disease, stroke/TIA. Both in clinical practice and in the published literature, the risk of ischemic stroke has been shown to vary depending on the specific NOAC used.[20-22] We observed that the use of low-dose rivaroxaban was associated with a higher rate of reaching the endpoint. Pairwise comparisons among groups receiving different types of NOACs and various dosages highlighted a noteworthy finding. Specifically, the significance observed can be attributed to the low-dose rivaroxaban treatment as each group exhibited a significant difference when compared to the low-dose rivaroxaban group. In contrast, no statistically significant disparities manifested among the remaining groups.

Multivariate analysis proved that several conditions such as congestive heart failure, prior stroke/TIA, and presence of vascular disease were also associated with a higher risk of reaching the endpoint. On the other hand, it should be noted that NOAC patients may not have been effectively anticoagulated. Non-vitamin K antagonist oral anticoagulants have relatively short half-lives, so missed doses result in loss of anticoagulation. Patients prescribed NOACs in routine clinical practice are often older, frail, and have multiple comorbidities, such as chronic kidney disease, making them more prone to bleeding and other adverse events. As a result, underdosing (appropriate or inappropriate) of NOACs is more common in real-world settings.[7,9,17,23] Inappropriate dosing of NOACs can result in major adverse cardiovascular events, including increased risk of stroke and/or systemic embolism, cardiovascular hospitalization, major bleeding, and all-cause mortality. National registries and studies have reported inappropriate NOAC dosing in real-life settings with a prevalence ranging from 12.8% to 39%. A recent meta-analysis reported an overall prevalence of inappropriate NOAC dosing of 24%. Differences in the prevalence of inappropriate dosing between real-world observational studies may be related to criteria for determining appropriate doses, geographic and clinical variations, patient and physician selection, and physician knowledge. Unfortunately, the registry used in this study did not include any information on patient compliance, making it difficult to evaluate this explanation against other potential causes, such as intrinsic differences in drug use among dosage-compliant patients. Therefore, monitoring of anticoagulation levels may be crucial.

Some studies have shown that the ATRIA stroke risk score predicts ischemic stroke better than the $CHADS_2$ and CHA_2DS_2-VASc risk prediction scores in patients with non-valvular AF.[24-26] In the Turkish population, the ATRIA score showed better predictive value than the R_2CHADS_2 and CHA_2DS_2-VASc scores. The R_2CHADS_2 score including renal function was more predictive than the CHA_2DS_2-VASc score but did not reach statistical significance. The superior performance of the ATRIA score is usually attributed to the inclusion of more age categories and a more complex but possibly more accurate weighting system. Although the ATRIA score is more complex than the $CHADS_2$ and CHA_2DS_2-VASc scores, this complexity can be easily overcome with widespread implementation of applications. The use of complex clinical scores and biomarkers has been found to improve the prediction of stroke risk in individuals with non-valvular AF. The ATRIA score has shown modest but statistically significant improvement in predicting stroke risk. Stroke risk should be viewed as a continuous spectrum rather than divided into fixed low, intermediate or high-risk categories, and that age is an important factor in this regard. The importance of regular reassessment of stroke risk due to the dynamic nature of risk factors, especially in older non-valvular AF patients with multiple other health conditions should be kept in mind. Patients with changes in their risk profile are more likely to have a stroke. Despite the fact that the ATRIA score provides better prediction capacity for experiencing stroke in several studies, including our work, the recent guidelines do not indicate favoring the ATRIA score over the $CHADS_2$ and CHA_2DS_2-VASc scores.[1,4]

Study Limitations

The study included fewer participants than the NOAC-TURK study because some centers did not participate, and some patients were lost to follow-up. Patients with indications for deep vein thrombosis and pulmonary thromboembolism who received NOAC were excluded, and some participants in the first step of the NOAC-TURK study could not be reached, leading to potential bias that could not be completely avoided. Edoxaban could not be included as the choice of NOAC drug depended on its time to market and reimbursement. Moreover, since the study was conducted only on patients using NOAC and the use of NOACs in patients with chronic kidney disease was limited, the success of risk scores, including renal function, may have been affected by the study design. As our article is based on real-life data, it was not feasible for us to assess the appropriateness of the dosages used or determine if they were appropriate or inappropriate. Instead, we focused on evaluating the medications prescribed by cardiologists in their routine practice, considering these doses to be suitable for the patients. The term "low dose" used in the study represents a quantitative expression as outlined in our research. While interpreting study findings, it is essential to acknowledge that patients burdened with a greater number of comorbidities inherently face an augmented risk of stroke, myocardial infarction, or mortality. Consequently, this subgroup of patients is managed with the prescription of low-dose medications. It is worth mentioning that due to the study's real-life design, a direct comparison of different patient groups receiving identical treatments was not feasible. Moreover, it is prudent to recognize that the study's results are specific to the geographic region in which the investigation was conducted. Extrapolating these findings to the global population may

result in unwarranted overestimation of the generalizability and applicability of the conclusions.

CONCLUSION

This prospective multicenter cross-sectional study investigated ischemic events and survival in NOAC-treated patients in Türkiye. Among NOAC types, low-dose rivaroxaban treatment was independently and strongly associated with the combined clinical endpoint. Furthermore, the ATRIA score proved to be a stronger predictor of stroke in the Turkish population.

Ethics Committee Approval: The study was approved by ethical commission of the Ethics Committee of Haydarpaşa Numune Training and Research Hospital (HNEAH-KAEK 2015/KK/60).

Informed Consent: All subjects gave written informed consent prior to inclusion.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – S.Ü., S.A., Ö.G., Ö.Ö., L.A., U.C., Ç.Y., A.Y.; Design – S.Ü., S.A., Ö.G., Ç.Y., A.Y., H.A.Ç.; Supervision – Ü.Y.S., M.Ş, S.P.; Resources – S.Ü., S.A., Ö.G., Ö.Ö., L.A., U.C., Ç.Y., A.Y., H.A.Ç., F.B.; Materials – S.Ü., S.A., Ö.G., Ö.Ö., L.A., U.C., Ç.Y., A.Y., H.A.Ç., F.B.; Data Collection and/or Processing – S.Ü., S.A., Ö.G., Ö.Ö., L.A., U.C., Ç.Y., A.Y., H.A.Ç., F.B.; Analysis and/or Interpretation – S.Ü., S.A., Ü.Y.S., M.Ş., S.P.; Literature Search – S.Ü., S.A., Ü.Y.S., M.Ş., S.P.; Writing – S.Ü., S.A., Ö.G.; Critical Review – Ü.Y.S., M.Ş., S.P.

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REFERENCES

1. Hindricks G, Potpara T, Dagres N, et al. ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): the Task Force for the diagnosis and management of atrial fibrillation of the Europea. *Eur Heart J* 2021;42(5):373-498. [CrossRef]
2. Steffel J, Collins R, Antz M, et al. European Heart Rhythm Association practical guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. *EP Eur.* 2021;23(10):1612-1676. [CrossRef]
3. Lip GYH, Nieuwlaat R, Pisters R, Lane DA, Crijns HJGM. 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(2):263-272. [CrossRef]
4. Singer DE, Chang Y, Borowsky LH, et al. A new risk scheme to predict ischemic stroke and other thromboembolism in atrial fibrillation: the ATRIA study stroke risk score. *J Am Heart Assoc*. 2013;2(3):e000250. [CrossRef]
5. Piccini JP, Stevens SR, Chang Y, et al. Renal dysfunction as a predictor of stroke and systemic embolism in patients with nonvalvular atrial fibrillation: validation of the R(2)CHADS(2) index in the ROCKET AF. *Circulation*. 2013;127(2):224-232. [CrossRef]
6. Başaran Ö, Beton O, Doğan V, et al. ReAl-life Multicenter Survey Evaluating Stroke prevention strategies in non-valvular atrial fibrillation (RAMSES study). *Anatol J Cardiol*. 2016;16(10):734-741. [CrossRef]
7. Shen NN, Zhang C, Hang Y, et al. Real-world prevalence of direct oral anticoagulant off-label doses in atrial fibrillation: an epidemiological meta-analysis. *Front Pharmacol*. 2021;12: 581293. [CrossRef]
8. Kocabas U, Kaya E, Avcı G. Novel oral anticoagulants in non-valvular atrial fibrillation: pharmacological properties, clinical trials, guideline recommendations, new antidote drugs and real-world data. *Int J Cardiovasc Acad*. 2016;2(4):167-173. [CrossRef]
9. Pham PN, Brown JD. Real-world adherence for direct oral anticoagulants in a newly diagnosed atrial fibrillation cohort: does the dosing interval matter? *BMC Cardiovasc Disord*. 2019;19(1):64. [CrossRef]
10. Altay S, Yıldırımtürk Ö, Çakmak HA, et al. New oral anticoagulants-TURKey (NOAC-TURK): multicenter cross-sectional study. *Anatol J Cardiol*. 2017;17(5):353-361. [CrossRef]
11. Gedikli Ö, Altay S, Ünlü S, 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(3):196-204. [CrossRef]
12. Easton JD, Saver JL, Albers GW, et al. Definition and evaluation of transient ischemic attack: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; and the Interdisciplinary Council on Peripheral Vascular Disease. The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists. *Stroke*. 2009;40(6):2276-2293. [CrossRef]
13. Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. *Eur Heart J*. 2012;33(20):2551-2567. [CrossRef]
14. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more 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(6): 461-470. [CrossRef]
15. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics*. 1988;44(3):837-845. [CrossRef]
16. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJGM, Lip GYH. 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(5):1093-1100. [CrossRef]
17. Kocabaş U, Ergin I, Yavuz V, et al. Real-world evaluation of anticoagulant treatment patterns in patients with atrial fibrillation: data from multicenter ROTA study. *Turk Kardiyol Dern Ars*. 2023;51(2):88-96. [CrossRef]
18. Kocabaş U, Ergin I, Yavuz V, et al. ANATOLIA-AF; study investigators. PrevAleNce and Associated factors of inappropriaTe dosing of direct Oral anticoaguLants In pAtients with Atrial Fibrillation: the ANATOLIA-AF Study. *Cardiovasc Drugs Ther*. 2022. [CrossRef]
19. Sayın B, Okutucu S, Yılmaz MB, et al. Antithrombotic treatment patterns and stroke prevention in patients with atrial fibrillation in TURKEY: inferences from GARFIELD-AF registry. *Anatol J Cardiol*. 2019;21(5):272-280. [CrossRef]
20. Zhang J, Tang J, Cui X, et al. Indirect comparison of novel Oral anticoagulants among Asians with non-valvular atrial fibrillation in the real world setting: a network meta-analysis. *BMC Cardiovasc Disord*. 2019;19(1):182. [CrossRef]

21. Loo SY, Coulombe J, Dell'Aniello S, Brophy JM, Suissa S, Renoux C. Comparative effectiveness of novel oral anticoagulants in UK patients with non-valvular atrial fibrillation and chronic kidney disease: a matched cohort study. *BMJ Open*. 2018;8(1):e019638. [CrossRef]
22. Zhu W, Ye Z, Chen S, et al. Comparative effectiveness and safety of non–vitamin K antagonist oral anticoagulants in atrial fibrillation patients. *Stroke*. 2021;52(4):1225-1233. [CrossRef]
23. Ntaios G, Papavasileiou V, Makaritsis K, Vemmos K, Michel P, Lip GYH. Real-world setting comparison of nonvitamin-K antagonist oral anticoagulants versus vitamin-K antagonists for stroke prevention in atrial fibrillation: a Systematic Review and Meta-Analysis. *Stroke*. 2017;48(9):2494-2503. [CrossRef]
24. van der Endt VHW, Milders J, Penning de Vries BBL, et al. Comprehensive comparison of stroke risk score performance: a systematic review and meta-analysis among 6 267 728 patients with atrial fibrillation. *Europace*. 2022;24(11):1739-1753. [CrossRef]
25. Yu I, Song TJ, Kim BJ, et al. CHADS2, CHA2DS2-VASc, ATRIA, and Essen stroke risk scores in stroke with atrial fibrillation: a nationwide multicenter registry study. *Med (Baltim)*. 2021;100(3):e24000. [CrossRef]
26. de Jong Y, Fu EL, van Diepen M, et al. Validation of risk scores for ischaemic stroke in atrial fibrillation across the spectrum of kidney function. *Eur Heart J*. 2021;42(15):1476-1485. [CrossRef]

Supplementary Table 1. Baseline characteristics of study patients grouped according to type of new oral anticoagulant agents used and meeting clinical endpoint

	Group without clinical endpoint (n=1621)						P	Group with clinical endpoint (n=186)						
Characteristic	**Dabigatran 150 mg bid (n=254)**	**Dabigatran 110 mg- bid (n=364)**	**Rivaroxaban 20 mg od (n=355)**	**Rivaroxaban 15 mg od (n=223)**	**Apixaban 5 mg bid (n=285)**	**Apixaban 2.5 mg bid (n=140)**		**Dabigatran 150 mg bid (n=19)**	**Dabigatran 110 mg- bid (n=45)**	**Rivaroxaban 20 mg od (n=30)**	**Rivaroxaban 15 mg od (n=53)**	**Apixaban 5 mg bid (n=23)**	**Apixaban 2.5 mg bid (n=16)**	**P**
Age (years)	68.3 ± 9.4#¥**	76 ± 9.2π¥*	68.6 ± 11Ω¥**	77.4 ± 9.2¥**	72 ± 9.2*	81.4 ± 5.9	< 0.001	73.5 ± 7.7#Ω*	79.3 ± 11.7π¥	73.5 ± 6.7Ω*	79.1 ± 7.9¥	75 ± 9.4*	83.3 ± 6.7	0.001
Age≥85 (n, (%))	82 (32)	43 (12)	101 (28)	22 (10)	57 (20)	1 (1)	< 0.001	2 (11)	3 (7)	3 (10)	1 (0)	3 (10)	0 (0)	0.008
Age 75-84 (n, (%))	108 (43)	87 (24)	146 (41)	48 (20)	100 (40)	19 (14)		9 (47)	10 (22)	15 (50)	15 (30)	6 (30)	1 (6)	
Age 65-74 (n, (%))	56 (22)	185 (51)	92 (26)	99 (40)	114 (40)	73 (52)		7 (37)	15 (33)	11 (37)	23 (40)	10 (40)	9 (56)	
Age < 65 (n, (%))	8 (3)	49 (13)	16 (5)	54 (20)	14 (0)	47 (34)		1 (5)	17 (38)	1 (3)	14 (30)	4 (20)	6 (38)	
Female (n, (%))	151 (59.4)	220 (60.4)	220 (62)	134 (60.1)	178 (62.5)	95 (67.9)	0.647	19 (73.7)	45 (62.2)	30 (40)	53 (58.5)	23 (56.5)	16 (62.5)	0.269
Baseline comorbidities														
Previous stroke,TIA (n, (%))	37 (14.6)	42 (11.5)	34 (9.6)	27 (12.1)	19 (6.7)	14 (10)	0.072	3 (15.8)	12 (26.7)	2 (6.7)	11 (20.8)	8 (34.8)	4 (25)	0.184
Diabetes mellitus (n, (%)	61 (24)	93 (25.5)	66 (18.6)	35 (15.7)	61 (21.4)	28 (20)	0.053	3 (15.8)	12 (26.7)	5 (16.7)	8 (15.1)	4 (17.4)	6 (37.5)	0356
Hyperlipidemia (n, (%))	122 (48)	185 (50.8)	166 (46.8)	97 (43.5)	124 (43.5)	58 (41.4)	0.282	5 (26.3)	14 (31.1)	13 (43.3)	19 (35.8)	8 (34.8)	11 (68.8)	0.085
Hypertension (n, (%))	214 (84.3)	328 (90.1)	279 (78.6)	204 (91.5)	243 (85.3)	130 (92.9)	< 0.001	17 (89.5)	38 (84.4)	25 (83.3)	46 (86.8)	18 (78.3)	16 (100)	0.515
Coronary artery disease (n, (%))	55 (21.7)	94 (25.8)	85 (23.9)	68 (30.5)	81 (28.4)	53 (37.9)	0.008	2 (10.5)	7 (15.6)	6 (20)	16 (30.2)	8 (34.8)	8 (50)	0.037
Chronic heart failure (n, (%))	56 (22)	97 (26.6)	91 (25.6)	70 (31.4)	81 (28.4)	54 (38.6)	0.011	5 (26.3)	14 (31.1)	10 (33.3)	27 (50.9)	10 (43.5)	7 (43.8)	0.272
Chronic renal failure (n, (%))	6 (2.4)	37 (10.2)	14 (3.9)	32 (14.3)	27 (9.5)	23 (16.4)	< 0.001	3 (15.8)	5 (11.1)	4 (13.3)	14 (26.4)	2 (8.7)	0 (0)	0.089
Peripheral artery disease (n, (%))	28 (11)	37 (10.2)	34 (9.6)	22 (9.9)	12 (4.2)	9 (6.4)	0.042	0 (0)	6 (13.3)	2 (6.7)	0 (0)	1 (4.3)	0 (0)	0.038
GFR (mL/min/1.73 m^2)	84.1 ± 21.7#Ω*	74 ± 19.8π¥*	82 ± 20.9Ω*	72.5 ± 21.6¥	82.5 ± 20.8*	74.6 ± 19.5	< 0.001	80.4 ± 24.7	74.6 ± 20.5	73 ± 23.5	69.5 ± 20.4	80.1 ± 20.6	74.8 ± 15.8	0.318
GFR groups														
< 30 (n, (%))	1 (0.4)	2 (0.5)	1 (0.3)	2 (0.9)	0 (0)	2 (1.4)	< 0.001	0 (0)	5 (11.1)	2 (6.7)	1 (1.9)	0 (0)	0 (0)	0.338
30-60 (n, (%))	30 (11.8)	80 (22)	43 (12.1)	62 (27.8)	38 (13.3)	27 (19.3)		3 (15.8)	12 (26.7)	8 (26.7)	18 (34)	5 (21.7)	3 (18.8)	
60-90 (n, (%))	115 (45.3)	211 (58)	186 (52.4)	105 (47.1)	141 (49.5)	84 (60)		11 (57.9)	17 (37.8)	12 (40)	25 (47.2)	11 (47.8)	11 (68.8)	
>90 (n, (%))	108 (42.5)	71 (19.5)	125 (35.2)	54 (24.2)	106 (37.2)	27 (19.3)		5 (26.3)	11 (24.4)	8 (26.7)	9 (17)	7 (30.4)	2 (12.5)	
CHA2DS2-VASC score														
Mean	3.4 ± 1.4#Ω*	4.1 ± 1.5π¥*	3.4 ± 1.5Ω*	4.2 ± 1.4¥*	3.7 ± 1.4*	4.6 ± 1.4	< 0.001	3.8 ± 1.3*	4.5 ± 1.4π	3.4 ± 1.4Ω*	4.5 ± 1.5	4.5 ± 1.7	5.4 ± 1.5	0.001
CHA2DS2-VASC score (n, (%))														
0	2 (0.8)	2 (0.5)	4 (1.1)	0 (0)	1 (0.4)	0 (0)	< 0.001	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0.166
1	14 (5.5)	12 (3.3)	28 (7.9)	5 (2.2)	12 (4.2)	0 (0)		0 (0)	1 (2.2)	3 (10)	1 (1.9)	1 (4.3)	0 (0)	
2	54 (21.3)	28 (7.7)	72 (20.3)	19 (8.5)	44 (15.4)	6 (4.3)		3 (15.8)	1 (2.2)	3 (10)	5 (9.4)	0 (0)	0 (0)	
3	73 (28.7)	84 (23.1)	89 (25.1)	41 (18.4)	79 (27.7)	20 (14.3)		5 (26.3)	6 (13.3)	9 (30)	7 (13.2)	6 (26.1)	1 (6.3)	
4	59 (23.2)	98 (26.9)	93 (26.2)	74 (33.2)	81 (28.4)	46 (32.9)		6 (31.6)	17 (37.8)	11 (36.7)	14 (26.4)	7 (30.4)	4 (25)	
5	34 (13.4)	84 (23.1)	40 (11.3)	51 (22.9)	42 (14.7)	34 (24.3)		3 (15.8)	10 (22.2)	2 (6.7)	10 (18.9)	3 (13)	4 (25)	
6	15 (5.9)	36 (9.9)	20 (5.6)	21 (9.4)	16 (5.6)	21 (15)		1 (5.3)	6 (13.3)	1 (3.3)	12 (22.6)	2 (8.7)	4 (25)	
7	1 (0.4)	13 (3.6)	8 (2.3)	9 (4)	7 (2.5)	10 (7.1)		1 (5.3)	3 (6.7)	1 (3.3)	3 (5.7)	3 (13)	2 (12.5)	
8	2 (0.8)	4 (1.1)	1 (0.3)	3 (1.3)	2 (0.7)	1 (0.7)		0 (0)	1 (2.2)	0 (0)	1 (1.9)	1 (4.3)	0 (0)	
9	0 (0)	3 (0.8)	0 (0)	0 (0)	1 (0.4)	2 (1.4)		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (6.3)	

(*Continued*)

Supplementary Table 1. Baseline characteristics of study patients grouped according to type of new oral anticoagulant agents used and meeting clinical endpoint (*Continued*)

	Group without clinical endpoint (n=1621)						P	Group with clinical endpoint (n=186)						
Characteristic	Dabigatran 150 mg bid (n=254)	Dabigatran 110 mg- bid (n=364)	Rivaroxaban 20 mg od (n=355)	Rivaroxaban 15 mg od (n=223)	Apixaban 5 mg bid (n=285)	Apixaban 2.5 mg bid (n=140)		Dabigatran 150 mg bid (n=19)	Dabigatran 110 mg- bid (n=45)	Rivaroxaban 20 mg od (n=30)	Rivaroxaban 15 mg od (n=53)	Apixaban 5 mg bid (n=23)	Apixaban 2.5 mg bid (n=16)	P
R2-CHA2DS score														
Mean														
R2-CHA2DS score (n, (%))	$2.1 \pm 1.3^{\#\Omega*}$	$2.8 \pm 1.5^{\pi¥}$	$2 \pm 1.3^{\Omega*}$	$2.9 \pm 1.5^{¥}$	$2.2 \pm 1.3^{*}$	$3 \pm 1.4^{\#\pi\Omega¥*}$	< 0.001	2.5 ± 1.1	$3.6 \pm 1.4^{\pi}$	2.5 ± 1.5	3.5 ± 1.7	3.2 ± 1.9	3.6 ± 1.5	0.013
0	15 (5.9)	8 (2.2)	32 (9)	4 (1.8)	13 (4.6)	0 (0)	< 0.001	0 (0)	0 (0)	2 (6.7)	0 (0)	0 (0)	0 (0)	0.163
1	79 (31.1)	58 (15.9)	110 (31)	27 (12.1)	77 (27)	13 (9.3)		3 (15.8)	2 (4.4)	5 (16.7)	6 (11.3)	5 (21.7)	0 (0)	
2	80 (31.5)	125 (34.3)	111 (31.3)	82 (36.8)	101 (35.4)	50 (35.7)		8 (42.1)	10 (22.2)	10 (33.3)	11 (20.8)	5 (21.7)	5 (31.3)	
3	45 (17.7)	69 (19)	56 (15.8)	32 (14.3)	51 (17.9)	34 (24.3)		5 (26.3)	9 (20)	6 (20)	13 (24.5)	3 (13)	3 (18.8)	
4	23 (9.1)	52 (14.3)	29 (8.2)	50 (22.4)	28 (9.8)	23 (16.4)		2 (10.5)	15 (33.3)	4 (13.3)	8 (15.1)	4 (17.4)	3 (18.8)	
5	9 (3.5)	36 (9.9)	12 (3.4)	16 (7.2)	9 (3.2)	10 (7.1)		1 (5.3)	4 (8.9)	2 (6.7)	7 (13.2)	4 (17.4)	3 (18.8)	
6	2 (0.8)	13 (3.6)	5 (1.4)	7 (3.1)	3 (1.1)	8 (5.7)		0 (0)	4 (8.9)	0 (0)	4 (7.5)	0 (0)	2 (12.5)	
7	0 (0)	3 (0.8)	0 (0)	5 (2.2)	2 (0.7)	1 (0.7)		0 (0)	1 (2.2)	1 (3.3)	4 (7.5)	2 (8.7)	0 (0)	
8	1 (0.4)	0 (0)	0 (0)	0 (0)	1 (0.4)	1 (0.7)		(0)	(0)	(0)	(0)	(0)	(0)	
HAS-BLED score														
Mean	$1.8 \pm 1^{\#\Omega*}$	$2.1 \pm 1.1^{\pi¥}$	$1.8 \pm 1.1^{\Omega*}$	$2.3 \pm 1.1^{¥}$	$1.7 \pm 1^{*}$	2.2 ± 1.1	< 0.001	1.8 ± 1.2	2.5 ± 0.9	2.2 ± 1	2.6 ± 1.1	2 ± 1.2	2.4 ± 1.2	0.078
HAS-BLED score groups (n, (%))														
0- 1 Low	102 (40.2)	96 (26.4)	134 (37.7)	48 (21.5)	112 (39.3)	38 (27.1)	< 0.001	7 (36.8)	7 (15.6)	6 (20)	9 (17)	9 (39.1)	2 (12.5)	0.072
2 Moderate	80 (31.5)	149 (40.9)	128 (36.1)	81 (36.3)	124 (43.5)	54 (38.6)		8 (42.1)	15 (33.3)	12 (40)	13 (24.5)	7 (30.4)	8 (50)	
3-5 High bleeding risk	72 (28.3)	117 (32.1)	93 (26.2)	93 (41.7)	49 (17.2)	47 (33.6)		4 (21.1)	23 (51.1)	12 (40)	31 (58.5)	7 (30.4)	6 (37.5)	
>5* Very high	0 (0)	2 (0.5)	0 (0)	1 (0.4)	0 (0)	1 (0.7)		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	
ATRIA score														
Mean	$5.3 \pm 2.6^{\#\Omega*}$	$6.5 \pm 2.3^{\pi¥*}$	$5.1 \pm 2.6^{\Omega*}$	$6.8 \pm 2.3^{¥*}$	$5.6 \pm 2.4^{*}$	7.6 ± 1.7	< 0.001	$6.3 \pm 2.1^{\#}$	$8.2 \pm 2.2^{\pi\Omega}$	$5.7 \pm 2.2^{\Omega¥*}$	7.8 ± 2.2	7.6 ± 3	$8.5 \pm 1.3^{\#\pi\Omega¥*}$	< 0.001
ATRIA score groups (n, (%))	134 (52.8)	100 (27.5)	200 (56.3)	51 (22.9)	127 (44.6)	15 (10.7)								
Low risk of stroke (< 1%): 0-5 points	37 (14.6)	54 (14.8)	42 (11.8)	33 (14.8)	52 (18.2)	15 (10.7)	< 0.001	7 (36.8)	4 (8.9)	12 (40)	5 (9.4)	5 (21.7)	0 (0)	0.001
Intermediate risk of stroke (1- < 2%): 6 points	83 (32.7)	210 (57.7)	113 (31.8)	139 (62.3)	106 (37.2)	110 (78.6)		2 (10.5)	3 (6.7)	5 (16.7)	5 (9.4)	2 (8.7)	1 (6.3)	
High risk of stroke (≥2%): >6 points	134 (52.8)	100 (27.5)	200 (56.3)	51 (22.9)	127 (44.6)	15 (10.7)		10 (52.6)	38 (84.4)	13 (43.3)	43 (81.1)	16 (69.6)	15 (93.8)	

GFR - glomerular filtration rate;ASA; acetylsalicylic acid.
ANOVA test was used for continuous variables with post-Hoc Bonferroni correction. Categorical variables were compared by the x^2 test. For post-hoc analysis results are shown as; $^{\#}$ significantly different Dabigatran 110mg group, $^{\pi}$ significantly different from Rivaroxaban 20mg group, $^{\Omega}$ significantly different from Rivaroxaban 15mg group, $^{¥}$ significantly different from apixaban 5mg group, *significantly different from apixaban 2.5mg group.