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Real-World Evaluation of Anticoagulant Treatment Patterns in Patients with Atrial Fibrillation: Data from Multicenter ROTA Study

Atriyal Fibrilasyon Hastalarında Gerçek Yaşam Antikoagülan Tedavi Tercihlerinin Değerlendirilmesi: Çok Merkezli ROTA Çalışması Verileri

ORIGINAL ARTICLE
KLİNİK ÇALIŞMA

Umut Kocabaş[1]
Işıl Ergin[2]
Veysel Yavuz[3]
Selda Murat[4]
Ibrahim Özdemir[5]
Ömer Genç[6]
Cihan Altın[7]
Haşim Tüner[8]
Bengisu Keskin Meriç[9]
Ali Çoner[10]
Elif İlkay Yüce[11]
Bedrettin Boyraz[12]
Onur Aslan[13]
Ahmet Dal[7]
Taner Şen[14]
Ersin İbişoğlu[15]
Aslan Erdoğan[15]
Mehmet Özgeyik[16]
Mevlüt Demir[14]
Ziya Gökalp Bilgel[17]
Büşra Güvendi Şengör[18]
Örsan Deniz Urgun[19]
Mustafa Doğduş[20]
Deniz Dilan Naki Tekin[15]
Sinem Çakal[21]
Sercan Çayırlı[22]
Arda Güler[23]
Dilay Karabulut[24]
Onur Dalgıç[25]
Osman Uzman[26]
Bektaş Murat[16]
Şeyda Şahin[27]
Umut Karabulut[28]
Tarık Kıvrak[29]
Muharrem Said Coşgun[30]
Ferhan Özyurtlu[31]
Mehmet Kaplan[32]
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ABSTRACT

Objective: Oral anticoagulant therapy is the cornerstone of atrial fibrillation management to prevent stroke and systemic embolism. However, there is limited real-world information regarding stroke and systemic embolism prevention strategies in patients with atrial fibrillation. The aim of the ROTA study is to obtain the real-world data of anticoagulant treatment patterns in patients with atrial fibrillation.

Materials and Methods: The ROTA study is a prospective, multicenter, and observational study that included 2597 patients with atrial fibrillation. The study population was recruited from 41 cardiology outpatient clinics between January 2021 and May 2021.

Results: The median age of the study population was 72 years (range: 22-98 years) and 57.4% were female. The median CHA_2DS_2-VASc and HAS-BLED scores were 4 (range: 0-9) and 1 (range: 0-6), respectively. Vitamin K antagonists and direct oral anticoagulants were used in 15.9% and 79.4% of patients, respectively. The mean time in therapeutic range was 52.9% for patients receiving vitamin K antagonists, and 76% of those patients had an inadequate time in therapeutic range with <70%. The most common prescribed direct oral anticoagulants were rivaroxaban (38.1%), apixaban (25.5%), and edoxaban (11.2%). The rate of overuse of vitamin K antagonists and direct oral anticoagulants was high (76.1%) in patients with low stroke risk, and more than one-fourth of patients on direct oral anticoagulant therapy were receiving a reduced dose of direct oral anticoagulants. Among patients who were on direct oral anticoagulant treatment, patients with apixaban treatment were older, had higher CHA_2DS_2-VASc and HAS-BLED scores, and had lower creatinine clearance than the patients receiving other direct oral anticoagulants.

Conclusions: The ROTA study provides important real-world information about anticoagulant treatment patterns in patients with atrial fibrillation.

Keywords: Atrial fibrillation, anticoagulation, direct oral anticoagulants, stroke, systemic embolism

ÖZET

Amaç: Atriyal fibrilasyon (AF) hastalarında inme ve sistemik emboliyi önlemek için kullanılan oral antikoagülan tedaviler AF yönetiminin temel taşıdır. Bununla birlikte, AF hastalarında inme ve sistemik emboli önleme stratejilerine ilişkin ülkemize ait gerçek yaşam verisi sınırlıdır. ROTA çalışmasının amacı, AF hastalarında antikoagülan tedavi stratejilerine ilişkin gerçek yaşam verilerini verilerini elde etmektir.

Yöntemler: ROTA çalışması, 2597 AF hastasının dahil edildiği ileriye dönük, çok merkezli ve gözlemsel bir çalışmadır. Çalışma popülasyonu, Ocak 2021-Mayıs 2021 tarihleri arasında 41 kardiyoloji merkezi tarafından çalışmaya dahil edilmiştir.

Bulgular: Çalışma popülasyonunun %57,4'ü kadın ve ortanca yaşı 72 (aralık: 22-98 yaş) idi. Ortanca CHA_2DS_2-VASc ve HAS-BLED skorları sırasıyla 4 (aralık: 0-9) ve 1 (aralık: 0-6) idi. Hastaların %15,9'u vitamin K antagonisti (VKA) ve %79,4'ü direkt oral antikoagülan (DOAK) tedavi alıyordu. VKA alan hastalarda ortalama terapötik aralıkta geçen sure %52,9 iken, bu hastaların %76'sının terapötik aralıkta geçen zaman yüzdesi %70 ve altında idi. En sık kullanılan DOAK tedavileri rivaroksaban (%38,1), apiksaban (%25,5) ve edoksaban (%11,2) idi. Düşük inme riskine sahip hasta grubunda VKA ve DOAK kullanım oranı yüksek idi (%76,1). Hastaların dörtte birinden fazlası düşük doz DOAK tedavisi almaktaydı. DOAK tedavisi alan hasta grubunda, apiksaban kullanan hastalar diğer DOAK tedavilerini kullanan hastalara kıyasla daha

yaşlı idi, daha yüksek CHA_2DS_2-VASc ve HAS-BLED skorlarına sahipti ve kreatinin klirensi değerleri daha düşüktü.

Sonuç: ROTA çalışması, AF hastalarında antikoagülan tedavi seçimleri hakkında önemli gerçek yaşam verisi sunmaktadır.

Anahtar kelimeler: Atriyal fibrilasyon, antikoagülasyon, direct oral antikoagülanlar, inme, sistemik embolizm.

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in clinical practice and global prevalence of AF is between 2% and 4%.[1] Atrial fibrillation is associated with a 5-fold increased risk of stroke and systemic embolism.[1] Oral anticoagulant therapy, including vitamin K antagonists (VKAs) and direct oral anticoagulants (DOACs), is the cornerstone of AF management to prevent stroke and systemic embolism.[1,2]

Although VKAs have been used for preventing stroke and systemic embolism in patients with AF for more than 50 years, the use of VKAs in daily practice is challenging due to their narrow therapeutic index, the need for close monitoring, delayed onset and offset of anticoagulation, and several food and drug interactions.[2] More importantly, the safety and efficacy of VKAs mainly depend on the time in therapeutic range indicating the quality of anticoagulation. Although current guidelines recommend a time in therapeutic range of more than 70% for patients receiving VKAs, observational studies showed inadequate time in therapeutic range in routine clinical practice in many countries.[1,3,4]

The DOACs have been developed with the aim of overcoming these several limitations of VKAs. In 4 pivotal randomized controlled trials, dabigatran, rivaroxaban, apixaban, and edoxaban have demonstrated non-inferiority and/or superiority to warfarin in the prevention of stroke and systemic embolism.[5-8] All 4 DOACs are approved for preventing stroke and systemic embolism in patients with AF and 1 or more risk factors for stroke by regulatory authorities based on their pivotal phase III non-inferiority trials. Recently published AF guidelines recommend DOACs in preference to VKAs excluding patients with mechanical heart valves or moderate-to-severe mitral stenosis.[1,9] The management to prevent stroke and systemic embolism in patients with AF has been changed since the first prescription of dabigatran in Turkey in 2013, and the proportion of patients with AF receiving DOAC therapy has been rising continuously, reaching 37% in 2016.[10] Therefore, the collection of current data from the real-life registry is crucial to understand actual stroke and systemic embolism prevention strategies in patients with AF in Turkey.

The main goal of the ROTA study is to obtain real-world data on anticoagulant treatment patterns in patients with AF and to describe the demographic and clinical characteristics of those patients.

Materials and Methods

The ROTA study is a national, prospective, multicenter, and observational study that included patients with AF. Patients were recruited from cardiology outpatient clinics in 7 geographical regions of Turkey, including 11 university hospitals, 11 education and research hospitals, 15 state hospitals, and 4 private hospitals (supplementary material). Patients older than 18 years with a diagnosis of AF were included in this study. Patients with AF with moderate-to-severe mitral stenosis and/or mechanical heart valve and patients aged <18 years were excluded. The study population included 2782 patients enrolled by 48 cardiologists at 41 sites from January 2021 to May 2021. We excluded 185 patients (182 patients with mechanical valves and/or moderate-to-severe mitral stenosis and 3 patients with missing data). Of the enrolled patients, 2597 were eligible for inclusion and final analysis.

The patient's demographic, clinical, and laboratory data including age, sex, body mass index, AF type, medical history and comorbidities, renal function (serum creatinine levels and creatinine clearance), previous bleeding history, and anticoagulant treatments were collected at the first visit and recorded in a case report form with standardized definitions for all fields. CHA_2DS_2-VASc score (congestive heart failure or left ventricular dysfunction, hypertension, age ≥75 or 65–74 years, diabetes, history of stroke and/or systemic embolism, vascular

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disease, and sex); and HAS-BLED (hypertension, renal failure and/or liver failure, history of stroke, bleeding history, labile international normalized ratio, age >65 years, concomitant drug use that predisposing to bleeding and/or excessive alcohol use) score were calculated for each study patient for assessing thrombotic and bleeding risk.[1] In addition, the time in therapeutic range was calculated with the Rosendaal method for patients who were receiving VKAs for assessing the quality of anticoagulation.[11] Major bleeding was defined as fatal bleeding, and/or symptomatic bleeding in a critical area or organ (intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome), and/or bleeding leading to a decrease in hemoglobin level to at least 2.0 g/L or the need for transfusion of at least 2 units of erythrocyte suspension. Clinically relevant nonmajor bleeding was defined as clinically overt bleeding that requires medical attention. Minor bleeding was defined as other overt bleeding events that do not meet the criteria for major bleeding or clinically relevant nonmajor bleeding.[1]

The study was conducted in accordance with the principles of the Declaration of Helsinki, and all patients gave written informed consent to participate. This study was approved by the Ethics Committee of Başkent University (Approval No: KA20/463 and E-94603339-604.01.02-1547)

Statistical Analysis

Data collected were reported as either mean (± standard deviation) or median (interquartile range) according to the normality of distribution for continuous variables tested with 1-sample Kolmogorov–Smirnov test. For categorical variables, frequencies were presented as percentages. The Kruskal–Wallis test was used to compare median values of age, BMI, CHA_2DS_2-VASc score, HAS-BLED score, serum creatinine, and creatinine clearance (the normality of the distribution was rejected for all) among the 5 anticoagulant treatment types followed by post hoc testing using unpaired Mann–Whitney *U*-tests with a Bonferroni-adjusted alpha level ($P < 0.01$). The frequencies of categorical variables were compared using Pearson χ^2 or Fisher's exact test, when appropriate. All statistical analyses were performed using Statistical Package for Social Sciences version 23 for Windows (SPSS Inc., Chicago, Ill, USA). $P < 0.05$ was considered significant.

Results

Baseline demographic and clinical characteristics of the study population are presented in Table 1. The median age of the study population was 72 years (range: 22-98 years) and 57.4% were female. Permanent AF was present in 51.5% of patients, while 30.1% had paroxysmal AF and 13.9% had persistent or long-standing persistent AF. The most common comorbidities were hypertension, congestive heart failure, coronary artery disease, and diabetes mellitus (Table 1).

The median CHA_2DS_2-VASc score was 4 (range: 0-9) and 85.6% of patients had high stroke risk (CHA_2DS_2-VASc score ≥ 2 for males and ≥3 for females) (Figure 1). The median HAS-BLED score was 1 (range 0-6) and 85.9% of patients had HAS-BLED bleeding risk scores of <3. The time in therapeutic range was calculated for 408 of 412 patients with AF who were receiving VKA therapy. The mean time in therapeutic range was 52.9% in this study, and 76% of these patients had an inadequate time in therapeutic range (TTR) of <70% (Table 2).

Overall, 2484 patients with AF (95.6%) were receiving anticoagulant treatment for preventing stroke and systemic embolism. Among patients on oral anticoagulant treatment, 412 patients were receiving VKAs and 2062 patients were receiving DOACs

Table 1. Basal Characteristics of the Study Population (n = 2597)

Demographics	
Age, median (IQR), years	72 (13)
Age group, n (%)	
• <65 years	589 (22.7)
• 65-74 years	984 (37.9)
• ≥75 years	1024 (39.4)
Female, n (%)	1491 (57.4)
BMI, median (IQR), kg/m^2	28.04 (5.86)
Low body weight (≤60 kg), n (%)	242 (9.3)
Systolic BP, median (IQR), mmHg	130 (20)
Diastolic BP, median (IQR), mmHg	80 (15)
Heart rate, median (IQR), bpm	84 (26)
Laboratory data	
Serum creatinine, median (IQR), mg/dL	0.92 (0.37)
Creatinine clearance, median (IQR), mL/min	71.09 (34.9)
Hemoglobin, mean ± SD, mg/dL	13.01 ± 2.00
Medical history	
• Previous stroke and/or TIA, n (%)	382 (14.7)
• Myocardial infarction, n (%)	463 (17.8)
• Coronary artery disease, n (%)	842 (32.4)
• Congestive heart failure, n (%)	984 (37.9)
• Hypertension, n (%)	1994 (76.8)
• Diabetes mellitus, n (%)	743 (28.6)
• Dyslipidemia, n (%)	710 (27.3)
• Peripheral artery disease, n (%)	102 (3.9)
• OSAS, n (%)	99 (3.8)
• Anemia, n (%)	513 (9.8)
• Chronic liver disease, n (%)	26 (1)
• Current smoker, n (%)	433 (16.7)
• Cardioversion, n (%)	221 (8.5)
• AF ablation, n (%)	80 (3.1)
Previous bleeding history	
• Major bleeding, n (%)	88 (3.4)
• CRNM bleeding, n (%)	130 (5)
• Minor bleeding, n (%)	622 (24)

AF, atrial fibrillation; BMI, body mass index; BP, blood pressure; CRNM, clinically relevant non-major bleeding; IQR, interquartile range; OSAS, obstructive sleep apnea syndrome; SD, standard deviation; TIA, transient ischemic attack.

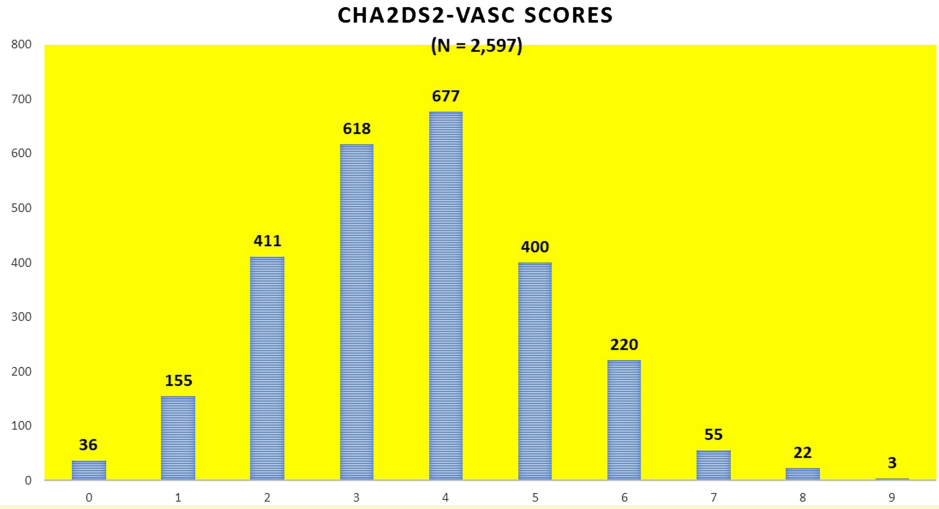

Figure 1. Number of patients according to the CHA_2DS_2-VASc score. CHA_2DS_2-VASc, congestive heart failure, hypertension, age ≥ 75 (2 points), diabetes, stroke (2 points), vascular disease, age 65-74, sex category (female).

(15.9% and 79.4%, respectively). The most commonly prescribed DOACs were rivaroxaban (38.1%) and apixaban (25.5.%) (Table 3 and Figure 2). The standard dose of DOAC was prescribed to 1486 patients (57.7%) and the reduced dose to 576 patients (22.2%). The proportion of patients receiving standard vs. reduced doses of each DOAC was 50.4% vs. 49.6% for dabigatran, 70.9% vs. 29.1% for rivaroxaban, 74.9% vs. 25.1% for apixaban, and 78.4% vs. 21.6% for edoxaban (Table 3 and Figure 3).

Table 2. Stroke and Bleeding Risk Scores and Time in Therapeutic Range Data (n=2597)

Variable	
CHA_2DS_2-VASc score, median (IQR)	4 (2)
CHA_2DS_2-VASc score class, n (%)	
• Low (score=0 for males and score=1 for females)	71 (2.7)
• Moderate (score=1 for males and score=2 for females)	303 (11.7)
• High (score ≥ 2 for males and score ≥ 3 for females)	2223 (85.6)
HAS-BLED score, median (IQR)	1 (1)
HAS-BLED score class, n (%)	
• Low (score < 3)	2230 (85.9)
• High (score ≥ 3)	366 (14.1)
• Missing	1 (<0.1)
Time in therapeutic range, mean ± SD, %#	52.9 ± 21.3
Time in therapeutic range class, n (%)#	
• Appropriate (TTR ≥70%)	98 (24)
• Inappropriate (TTR <70%)	310 (76)

CHA_2DS_2-VASc, congestive heart failure, hypertension, age ≥ 75 (2 points), diabetes, stroke (2 points), vascular disease, age 65-74, sex category (female); HAS-BLED, uncontrolled hypertension, abnormal renal and liver function (1 point each), stroke, bleeding, labile international normalized ratios, elderly (age > 65 years), drugs or alcohol (1 point each) (concomitant use of antiplatelet agents or non-steroidal anti-inflammatory drugs, alcohol abuse); IQR, interquartile range; SD, standard deviation; TTR, time in therapeutic range.
#Available data for 408 of 412 patients who are receiving vitamin K antagonist treatment.

When assessing anticoagulant treatment patterns according to stroke risk, in patients with low stroke risk (CHA_2DS_2-VASc score=0 for males and score=1 for females), 23.9% (n=17) received no anticoagulant treatment and 76.1% (n=54) received VKAs or DOACs or low-molecular-weight heparin (LMWH). Among patients with high stroke risk (CHA_2DS_2-VASc score ≥ 2 for males and score ≥ 3 for females), 3.5% (n=78) received no anticoagulant treatment and 96.5% (n=2145) received VKAs or DOACs or LMWH (Figure 4).

Among the study population, 394 patients (15.2%) were receiving antiplatelet therapy including aspirin, clopidogrel, ticagrelor, and prasugrel. The most commonly prescribed antiplatelet therapies were aspirin (9.7%) and clopidogrel (5.2%). The main prescribed drugs for rate control were beta-blockers, digoxin, and diltiazem (74.5%, 14.7%, and 11.1%, respectively) and for rhythm control were amiodarone and propafenone (4.7% and 4.1%, respectively) (Table 3).

Patients who were receiving VKAs were younger than those patients on DOACs. Among patients who were on DOAC treatment, patients who were administered apixaban were older than those treated with rivaroxaban or edoxaban. Additionally, the mean CHA_2DS_2-VASc score was significantly higher in patients who were receiving apixaban than those receiving VKAs or rivaroxaban or edoxaban. The mean HAS-BLED score was lower in patients with rivaroxaban or edoxaban treatment than in those with apixaban treatment. Creatinine clearance was lower in patients who were receiving apixaban than in those administered rivaroxaban or edoxaban. The proportion of patients with a history of major and/or clinically relevant non-major bleeding and/or gastrointestinal bleeding was similar between treatment groups. Concomitant use of antiplatelet therapy was higher in patients who were administered VKAs than those patients on DOACs (Table 4).

Table 3. Anticoagulant and Other Medical Therapies of the Study Population (N=2597)

Anticoagulant therapy, n (%)	
VKAs	412 (15.9)
DOACs	2062 (79.4)
• Dabigatran	121 (4.6)
• Dabigatran 150 mg	61 (2.3)
• Dabigatran 110 mg	60 (2.3)
• Rivaroxaban	988 (38.1)
• Rivaroxaban 20 mg	701 (27)
• Rivaroxaban 15 mg	287 (11.1)
• Apixaban	661 (25.5)
• Apixaban 5 mg	495 (19.1)
• Apixaban 2.5 mg	166 (6.4)
• Edoxaban	292 (11.2)
• Edoxaban 60 mg	229 (8.8)
• Edoxaban 30 mg	63 (2.4)
LMWHs	10 (0.4)
No anticoagulant therapy	113 (4.4)
Antiplatelet therapy, n (%)	
• Aspirin	252 (9.7)
• Clopidogrel	134 (5.2)
• Ticagrelor	5 (0.2)
• Prasugrel	3 (0.1)
Drugs for rate and/or rhythm control, n (%)	
• Beta-blockers	1936 (74.5)
• Verapamil	31 (1.2)
• Diltiazem	289 (11.1)
• Digoxin	383 (14.7)
• Amiodarone	123 (4.7)
• Propafenone	106 (4.1)
• Sotalol	14 (0.5)
Other therapies, n (%)	
• ACE inhibitors or ARBs	1515 (58.3)
• ARNI	55 (2.1)
• MRAs	473 (18.2)
• Diuretics	1301 (50.1)
• DHP-CCB	488 (18.8.)
• Alpha blockers	73 (2.8)
• Statins	521 (20.1)
• PPIs	1276 (49.1)
• NSAIDs	273 (10.5)
• Steroids	32 (1.2)

ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; ARNI, angiotensin receptor–neprilysin inhibitor; DHP-CCB, dihydropyridine calcium-channel blockers; DOACs, direct oral anticoagulants; LMWHs, low-molecular-weight heparins; MRAs, mineralocorticoid receptor antagonists; NSAIDs, non-steroidal anti-inflammatory drugs; PPIs, proton pump inhibitors; VKAs, vitamin K antagonists.

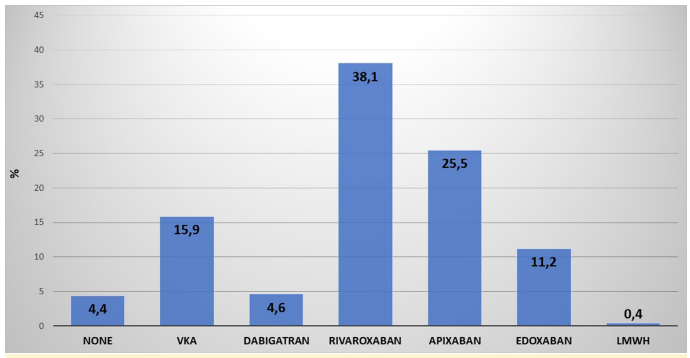

Figure 2. Frequency of anticoagulant treatments among the study population.

Discussion

The ROTA study provides important real-world information on the demographic, clinical, and management characteristics of patients with AF. The principal findings of this study are as follows: (1) the rate of prescribing of oral anticoagulants is high in Turkey with overall DOACs use higher than VKAs; (2) the rate of overuse of DOACs and VKAs is high in patients with a low stroke risk; (3) more than one-fourth of patients with AF on DOAC therapy receive reduced dose of DOACs; (4) only one-fourth of

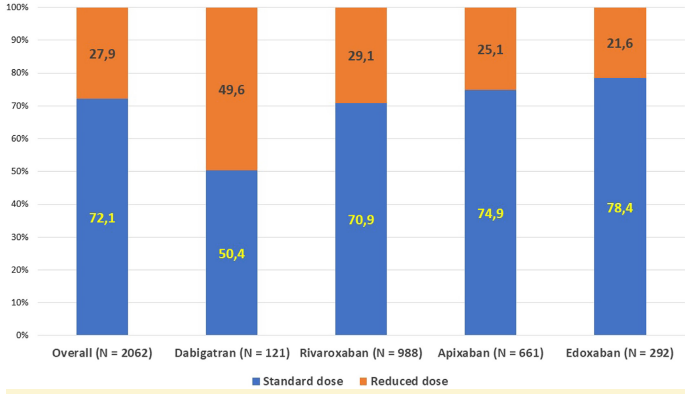

Figure 3. Frequency of standard versus reduced doses of direct oral anticoagulants.

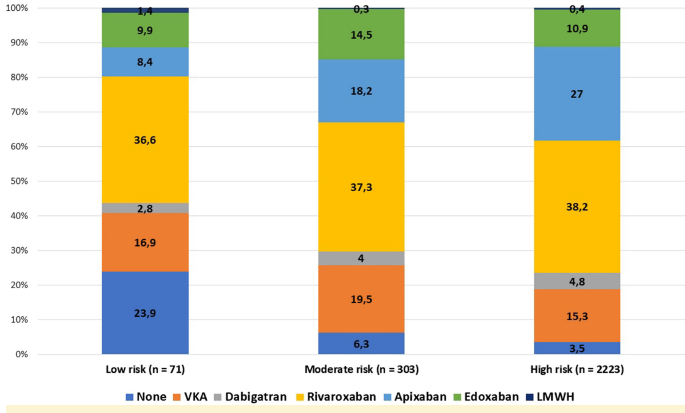

Figure 4. Anticoagulant treatment patterns according to the stroke risk profile.

Table 4. Comparison of Demographic and Clinical Characteristics of the Patients Stratified by Oral Anticoagulant

Variable	VKAs	Dabigatran	Rivaroxaban	Apixaban	Edoxaban	*P*	Test statistics
Age, mean ± SD, years	68.9 ± 10.3	72.1 ± 8.9	70.9 ± 10.0	73.0 ± 9.8	70.9 ± 11.1	<0.001*	47 179[a]
BMI, mean ± SD, kg/m^2	28.6 ± 4.4	29.4 ± 4.7	28.6 ± 4.8	28.7 ± 5.0	28.5 ± 4.8	0.383	4177[a]
CHA_2DS_2-VASc score, mean ± SD	3.4 ± 1.4	3.7 ± 1.5	3.5 ± 1.5	3.9 ± 1.4	3.5 ± 1.5	<0.001†	32
HAS-BLED score, mean ± SD	1.6 ± 1.1	1.5 ± 0.9	1.4 ± 0.8	1.6 ± 0.9	1.4 ± 0.9	<0.001‡	21 775[a]
Serum creatinine, mean ± SD, mg/dL	1.16 ± 0.94	0.97 ± 0.30	0.98 ± 0.35	1.03 ± 0.40	0.96 ± 0.31	0.074	8539[a]
Creatinine clearance, mean ± SD, mL/min	71 ± 28	72 ± 25	72 ± 24	69 ± 25	74 ± 23	0.014§	12 516[a]
History of major and/or CRNM bleeding, n (%)	29 (7)	11 (9.1)	68 (6.9)	60 (9.1)	26 (8.9)	0.443	3739[b]
History of GI bleeding, n (%)	22 (5.6)	7 (5.8)	45 (4.6)	45 (7)	12 (4.3)	0.297	4902[b]
Concomitant antiplatelet therapy, n (%)	60 (15.2)	8 (6.6)	123 (12.5)	69 (10.5)	29 (10.1)	0.046#	9701[b]

BMI, body mass index; CRNM, clinically relevant non-major bleeding; CHA_2DS_2-VASc, congestive heart failure, hypertension, age ≥ 75 (2 points), diabetes, stroke (2 points), vascular disease, age 65-74, sex category (female); GI, gastrointestinal; HAS-BLED, uncontrolled hypertension, abnormal renal and liver function (1 point each), stroke, bleeding, labile international normalized ratios, elderly (age > 65 years), drugs or alcohol (1 point each) (concomitant use of antiplatelet agents or non-steroidal anti-inflammatory drugs, alcohol abuse); IQR, interquartile range.
[a]Kruskal–Wallis test.
[b]Pearson's chi-square test.
*Significant for VKAs vs. dabigatran; VKAs vs. rivaroxaban; VKAs vs. apixaban; VKAs vs. edoxaban; rivaroxaban vs. apixaban; and apixaban vs. edoxaban.
†Significant for VKAs vs. apixaban; rivaroxaban vs. apixaban; and apixaban vs. edoxaban.
‡Significant for VKAs vs. rivaroxaban and rivaroxaban vs. apixaban.
§Significant for rivaroxaban vs. apixaban and apixaban vs. edoxaban.
#Significant for VKAs vs. other direct oral anticoagulants.

patients with AF on VKA therapy have adequate time in therapeutic range; and (5) patients who were receiving apixaban were older and had higher CHA_2DS_2-VASc and HAS-BLED scores and had lower creatinine clearance than those receiving other DOACs.

The previously published registries including the Western population have reported a mean age of >70 years in patients with AF.[12-14] In contrast, several studies conducted in Turkey have demonstrated that the mean age varies between 64 and 70 years in patients with AF.[10,15-17] In the Global Anticoagulant Registry in the FIELD-Atrial Fibrillation (GARFIELD-AF) registry, the proportion of older patients (≥75 years) who were enrolled from other countries was significantly higher than the proportion of older patients who were enrolled from Turkey (37.2% vs. 26.3%, respectively, $P=0.001$).[15] The median age (72 years) observed in our study is similar to that reported in published data from Western European countries or Northern America and is higher than previous Turkish registries which were published before 2017.[10,12-17] This considerable difference between the ROTA study and previous Turkish registries may be due to numerous reasons, including changing pattern of demographics in patients with AF, increasing elderly population in Turkey, and patient/center of selection of this study. Another important demographic difference observed in the ROTA study is the predominance of female patients. Although more than 55% of individuals are male in the phase III, randomized-controlled trials of DOACs and previous reports from the Western healthcare systems, 57.4% of the study population were female in this study.[5-7,12,18,19] Our results are in accordance with those of studies conducted in Turkey.[10,16,20] The TRAF study demonstrated that 57.1% of subjects were female which is similar to the ROTA study.[16] This difference might be related to the high prevalence of metabolic syndrome, obesity, sedentary lifestyle, and cardiovascular risk factors and/or diseases in Turkish women compared to the European population.[1,16,21] The mean CHA_2DS_2-VASc score varies between 3.2 and 4, and the mean HAS-BLED score varies between 1 and 1.6 in real-world studies.[10,12,14-16] The population-based cohort study comprising 507 136 subjects in Turkey reported that the median CHA_2DS_2-VASc score was 4 and the registry from Turkey reported that the mean HAS-BLED score was 1, which is similar to the present ROTA study.[15,16]

The results of the ROTA study show the changing pattern of anticoagulant treatment in patients with AF. Before the introduction of DOACs, the rate of prescribing VKAs was only 40% and the rate of prescribing antiplatelet therapy without VKAs was 42% in Turkey.[20] For the first time, in 2016, the ESC guideline for the management of AF restricted the use of antiplatelet therapy for preventing stroke and systemic embolism.[22] Additionally, DOACs are recommended in preference to VKAs in patients with AF with moderate-to-high stroke risk.[22] Before the publication of the ESC 2016 guideline, the global registries demonstrated that oral anticoagulants are not being used according to stroke risk scores with the underuse of oral anticoagulants in patients with

high stroke risk. The GARFIELD registry reported that 38% of patients with a $CHADS_2$ score ≥ 2 did not receive anticoagulant therapy.[23] In the EURObservational Research Programme in Atrial Fibrillation (EORP-AF) registry, the rate of prescribing DOACs was only 8.4%.[24] After the approval of the DOACs and publication of evidence-based guidelines, the observational studies reported that the use of DOACs increased and VKA decreased over time in patients with AF.[12,17] In Europe, the proportion of DOAC prescriptions increased from 53.4% to 75.8% and the proportion of VKA prescriptions decreased from 35.5% to 16.8% between 2012 and 2016.[25] In this analysis of the ROTA study, the rate of oral anticoagulant prescription is high and only 3.5% of patients with a high stroke risk did not receive oral anticoagulant treatment in a real-life setting. Another important observation revealed by this study is that compliance with guideline-based treatment recommendations for patients with AF has dramatically improved in Turkey within the past 5 years. In the Real-life Multicentre Survey Evaluating Stroke Prevention Strategies (RAMSES) study, the results of which were published in 2016, the rates of DOACs and VKAs use were 37% and 35%, respectively, in the outpatient population with AF.[10] In another study,[15] the rates of DOACs and VKAs use were 42.4% and 23.2%, respectively, in patients with AF, whereas the same rates were found to be 79.4% and 15.9%, respectively, in this study.

Although current guidelines do not recommend oral anticoagulant therapy in patients at low risk of stroke, evidence from real-life studies showed that overuse of VKAs and DOACs in those patients is high.[26] The prevalence of overuse of oral anticoagulant therapy in patients at low risk of stroke varies between 45% and 72% in Turkey.[10,15] In the ROTA study, more than 75% of patients at low stroke risk were receiving oral anticoagulant therapy. The overuse of oral anticoagulant therapy is associated with an increased risk of bleeding without a significant reduction in stroke and systemic embolism.[1,9] Therefore, physician awareness of stroke risk classification in patients with AF should be increased, and physicians should avoid to use oral anticoagulants in patients with AF at low stroke risk in our country.

The efficacy and safety of reduced doses of DOACs were tested in a small proportion of patients in the pivotal trials. Approximately 21% of the study population were receiving a reduced dose of rivaroxaban in the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) trial and only 4.7% of patients were taking a reduced dose of apixaban in the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial.[6,7] However, the results of observational studies in real-life settings are inconsistent with the results of these pivotal trials. The prevalence of the use of reduced doses varies between 29% and 56% in real-world studies.[13,17,27,28] In the ROTA study, the percentage of patients receiving reduced doses of DOACs is about 28% which is higher than pivotal trials and similar to other observational studies. The results of our study have demonstrated that dose reduction is more common in daily clinical practice than in randomized controlled trials. Inappropriate prescription of DOACs—in other words, the dose reduction without a true indication—is associated with an increased rate of stroke and systemic embolism and/or bleeding. This considerable difference in the prescription of reduced doses of DOACs between real-life practice and randomized controlled trials may be due to numerous reasons, including patient-related factors such as advanced age, frailty, and the presence of multiple comorbidities or physician-related factors such as lack of awareness about the appropriate doses of anticoagulant treatment and fear of side effects, and nonmedical factors such as the cost of medications, legislation on reimbursement for medications, and restriction of access to healthcare services. Physician awareness about recommendations of evidence-based AF guidelines should be increased, and physicians should be encouraged to prescribe appropriate doses of DOACs in patients with AF in our country.

The safety and efficacy of VKAs mainly depend on the time in therapeutic range indicating the quality of anticoagulation. Inappropriate anticoagulation assessed by time in therapeutic range is associated with adverse outcomes including hemorrhage, stroke, and death.[4] Current guidelines recommend a time in therapeutic range of more than 70% for patients receiving VKAs.[1] In the pivotal DOAC trials, the time in therapeutic range was 64% in RELY, 62% in ARISTOTLE, 55% in ROCKET-AF, and 68% in ENGAGE-AF TIMI-48.[5-8] However, optimal time in therapeutic range could not be achieved in patients on VKAs in real-life practice and observational studies showed lower time in therapeutic range values than randomized controlled trials. In Turkey, the mean time in therapeutic range varies between 40% and 54% in patients on VKA therapy.[4,20,29,30] A systematic meta-analysis including 11 studies and 10 501 patients showed that the average time in therapeutic range is 49.8% in Turkey.[31] In the ROTA study, the mean time in therapeutic range was found to be 52.9%, and 76% of patients on VKAs therapy had an inadequate TTR with <70%. The results of the ROTA study clearly demonstrate the poor quality of anticoagulation with VKAs in Turkey, and more than three-fourths of patients with AF on VKA therapy need to be switched to a DOAC according to the guideline recommendations.[1] There is no doubt that the main reason for the use of VKAs instead of DOACs is the reimbursement criterion of the Social Security Institution in Turkey. The reimbursement criterion of the Social Security Institution states that "if the target international normalized ratio cannot be kept between 2.0 and 3.0 with warfarin in at least three of the last 5 measurements made at least one week apart, warfarin may be discontinued and dabigatran or rivaroxaban or apixaban or edoxaban treatment can be started."[31] The poor quality of anticoagulation and low time in therapeutic range with warfarin therapy in the ROTA registry indicates that the recommendation of recent AF guidelines about time in therapeutic range with more than 70% and the reimbursement criterion of the Social Security Institution in Turkey is unrealistic in real-life settings. Anticoagulant treatment with VKAs or DOACs for the management of stroke and systemic embolism prevention in patients with AF is a medical decision. Thus, it should be left to the physician's choice without any restriction.[31] On the other hand, the ROTA study points out that there is a need for rapid and organized action to improve TTR such as education of patients or relatives, counseling, and more frequent and/or self-monitoring in patients on VKA treatment.

To date, there is no head-to-head randomized controlled trial comparing the efficacy and safety of different DOACs. Data from phase-IV trials and meta-analysis of observational studies

suggest that while DOACs have a similar effect on the risk of ischemic stroke and systemic embolism, apixaban is associated with decreased risk of major and clinically relevant non-major bleeding compared with other DOACs.[32-34] The results of the ROTA study showed that patients receiving apixaban were older, had higher CHA_2DS_2-VASc and HAS-BLED scores, and had lower creatinine clearance than the patients receiving other DOACs. Similar to our study results, previous real-world studies have also demonstrated that the patients receiving apixaban were older and had multiple comorbidities than the patients receiving other DOACs.[35-37] This could be explained by the frailty of patients due to advanced age, renal impairment and presence of other comorbidities. The participating cardiologists in the ROTA study who had concerns about bleeding may have chosen apixaban treatment in patients with high bleeding due to the safety profile of apixaban.

Limitations of the Study

The present study had some limitations. First, the most important limitation of the ROTA study is its observational design, which may have led to patient evaluation and/or patient selection bias. Second, the study population was enrolled from the cardiology outpatient clinics, and this population did not include those presenting at the family medicine and internal medicine outpatient clinics. Thus, patients included in the present study do not completely represent usual clinical practice. Third, although the present study was conducted in 7 geographical regions of Turkey, some geographic areas may have been underrepresented. Thus, the study population does not represent the general population in Turkey. Finally, the present study data were based on the documentation of demographics, medical history, and treatments during the first outpatient clinic visit, and follow-up data were not obtained. Thus, we could not be able to report the stroke, systemic embolism, bleeding, and mortality rates of the patients with AF. Because of these limitations, the results of this study should be interpreted carefully.

Conclusion

The ROTA study demonstrates that the prescription of oral anticoagulants for stroke prevention in patients with AF has improved dramatically within the past 5 years. The analysis of the present study showed that more than 90% of patients with AF receive oral anticoagulant treatment including VKAs and DOACs. The introduction of the DOACs into clinical practice has changed anticoagulant treatment patterns, and DOACs were more commonly prescribed than VKAs. Although the rate of oral anticoagulant use was satisfactory, the overuse of VKAs and DOACs in patients with low stroke risk was found to be high. Additionally, the use of low-dose DOACs is more common in daily clinical practice than in randomized controlled trials. Finally, the results of the ROTA study clearly demonstrate the poor quality of anticoagulation with VKAs.

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