

ReAl-life Multicenter Survey Evaluating Stroke prevention strategies in non-valvular atrial fibrillation (RAMSES study)

Özcan Başaran, Osman Beton¹, Volkan Doğan, Mehmet Tekinalp², Ahmet Çağrı Aykan³, Ezgi Kalaycıoğlu³, İsmail Bolat⁴, Onur Taşar⁵, Özgen Şafak⁶, Macit Kalçık⁷, Mehmet Yaman⁸, İbrahim Altun, Mustafa Özcan Soylu, Cevat Kıрма⁹, Murat Biteker and Collaborators*

Department of Cardiology, Faculty of Medicine, Muğla Sıtkı Kocman University, Muğla-Turkey; ¹Department of Cardiology, Faculty of Medicine, Sivas Cumhuriyet University, Sivas-Turkey; ²Department of Cardiology, Kahramanmaraş Necip Fazıl State Hospital, Kahramanmaraş-Turkey; ³Department of Cardiology, Trabzon Ahi Evren Chest Cardiovascular Surgery Education and Research Hospital, Trabzon-Turkey; ⁴Department of Cardiology, Fethiye State Hospital, Fethiye-Turkey; ⁵Department of Cardiology, Elazığ Education and Research Hospital, Elazığ-Turkey; ⁶Department of Cardiology, Burdur State Hospital, Burdur-Turkey; ⁷Department of Cardiology, İskilip Atif Hoca State Hospital, Çorum-Turkey; ⁸Department of Cardiology, Samsun Education and Research Hospital, Samsun-Turkey; ⁹Department of Cardiology, Kartal Koşuyolu Heart Education and Research Hospital, İstanbul-Turkey

ABSTRACT

Objective: Data regarding stroke prevention strategies in non-valvular atrial fibrillation (NVAF) are limited to vitamin K antagonists (VKAs). This study aimed to evaluate real-life stroke prevention strategies for NVAF patients in the era of non-VKA oral anticoagulants (NOACs).

Methods: We established a cross-sectional, multicenter, nationwide registry of NVAF patients. All consecutive atrial fibrillation (AF) patients and without mechanical heart valves or rheumatic mitral stenosis (but including those with any degree of mitral regurgitation) were enrolled in the ReAl-life Multicenter Survey Evaluating Stroke Prevention Strategies (RAMSES Study; ClinicalTrials.gov identifier NCT02344901) in Turkey. Baseline demographic data, medical history, and medications prescribed for NVAF treatment were collected. Univariate analyses were performed for continuous variables, and the chi-square test was used for categorical variables.

Results: In total, 6273 patients from 29 provinces of Turkey were enrolled in the study between February and May 2015, with the contribution of 83 investigators. The mean age was 69.6±10.7 years; 56% of the patients were females, and one-fifth of the patients had at least one comorbid disease, the most common being hypertension (69%). The mean CHA₂DS₂-VASc and HAS-BLED scores were 3.3±1.6 and 1.6±1.1, respectively. The rate of oral anticoagulant (OAC) therapy use was 72% (37% NOAC and 35% VKA).

Conclusion: The RAMSES study showed a higher prevalence of OAC use among NVAF patients than that reported in previous studies. Although NOACs were preferred over VKAs in daily cardiology practice, there is a need for improved OAC therapies for NVAF patients.

(*Anatol J Cardiol* 2016; 16: 734-41)

Keywords: atrial fibrillation, stroke, prevention, oral anticoagulant therapy

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in clinical practice and is associated with an increased risk of thromboembolic events (1). Antithrombotic drugs, especially oral anticoagulants (OACs), are the mainstay of therapy to prevent stroke in AF patients. Although vitamin K antagonists (VKAs) were the only available drugs for stroke prevention for decades, in recent years, numerous non-VKA OACs (NOACs) have been developed and marketed. The efficacy and

safety of NOACs have been demonstrated in large randomized controlled clinical trials (RCTs) in non-valvular AF (NVAF) patients (2–5). However, these trials may not reflect real-world clinical settings due to the selection of patients to be included (6): RCTs generally have standardized protocols with close monitoring of patients, and this can be an obstacle to the implementation of outcomes in routine clinical practice. Observational studies have been performed to overcome these limitations, but they have mainly focused on VKAs (7, 8). Large international multicenter registries have been established after the introduction

Address for correspondence: Dr. Özcan Başaran, Muğla Sıtkı Koçman Üniversitesi Tıp Fakültesi, Orhaniye Mah. Haluk Özsoy Cad., 48000/Muğla-Türkiye
Phone: +90 252 214 13 26 Mobile: +90 506 535 90 13 E-mail: basaran_ozcan@yahoo.com

Accepted Date: 14.01.2016 **Available Online Date:** 14.04.2016

©Copyright 2016 by Turkish Society of Cardiology - Available online at www.anatoljcardiol.com
DOI:10.14744/AnatolJCardiol.2016.6752



of NOACs, and the results of these studies will provide valuable insights into the clinical course of NVAF patients (9–11).

A large multicenter registry in Turkey has shown that the use of warfarin (the only available VKA in Turkey) was 40% among NVAF patients (12). However, this trial was conducted when the only available OAC was warfarin. A recent Turkish study showed 76% of patients who were on NOACs switched from long-term warfarin therapy (13). Considering the new available drugs and advances in AF management, there is a need for a contemporary study evaluating stroke prevention strategies in NVAF patients. The aim of ReAl-life Multicenter Survey Evaluating Stroke Prevention Strategies (RAMSES) study is to provide current data regarding stroke prevention strategies in Turkey in the era of NOACs. In this study, we present the baseline characteristics, stroke risk factors, use of OAC therapies, and concomitant medications of NVAF patients in the RAMSES study.

Methods

Study design

The RAMSES study (ClinicalTrials.gov identifier NCT02344901) was planned as a national, multicenter, cross-sectional registry. All data for each patient were collected during a single visit.

Setting and study population

The study was conducted in outpatient cardiology clinics. To ensure adequate geographic diversity in patients included in the study, the number of patients enrolled in each of the seven regions (Marmara, Aegean, Mediterranean, Central Anatolia, Black Sea, East Anatolia, and Southeast Anatolia) in Turkey was proportional to the population of that region. State hospitals, university hospitals, teaching and research hospitals, and private hospitals were included to represent all patients treated within the different health care settings. The study was initiated in February 2015, and the final patient was enrolled in May 2015.

At each site, consecutive patients aged ≥ 18 years with electrocardiographically confirmed AF were enrolled. The patients could be in sinus rhythm or AF at the time of enrollment, but an electrocardiographically confirmed AF episode should have occurred prior to enrollment. Patients with coronary artery disease (a history of percutaneous intervention or coronary artery bypass graft surgery), congestive heart failure, hypertension, diabetes mellitus, and renal failure were included. The exclusion criteria were having a mechanical heart valve or any degree of rheumatic mitral stenosis (14). Those with other valvular disorders, including any degree of mitral regurgitation, aortic stenosis, or aortic regurgitation, were included.

Data collection and outcomes

Patient characteristics were obtained by a survey recording demographic data, including age, sex, level of education, place of residence (rural or urban), status of smoking status, presence of chronic obstructive pulmonary disease, and type of AF. The

patients were also questioned about stroke-associated risk factors such as coronary heart disease (CHD), hypertension, diabetes mellitus, previous stroke, congestive heart failure (CHF), and vascular disease (prior myocardial infarction, peripheral artery disease, or aortic plaque). Subsequently, the patients' ongoing pharmacologic treatment for stroke prevention (antiplatelet, anticoagulant, or none) and antiarrhythmic drug therapies were recorded. Hemorrhagic events related to the current therapy were noted, with major bleeding defined as any bleeding event leading to hospital admission or bleeding that causes a fall in hemoglobin level of 2 g/dL or more and minor bleeding defined as non-major bleeding. Scores were obtained for three standard instruments for assessing stroke and bleeding risk in AF: CHADS₂ (which takes into account congestive heart failure or left ventricular dysfunction, hypertension, age ≥ 75 years, diabetes, thromboembolism, and a history of stroke); CHA₂DS₂-VASc (congestive heart failure or left ventricular dysfunction, hypertension, age ≥ 75 or 65–74 years, diabetes, thromboembolism or a history of stroke, vascular disease, and sex); and HAS-BLED (hypertension, renal or liver failure, stroke history, bleeding history, labile international normalized ratio (INR), age > 65 years, drugs predisposing to bleeding, and alcohol use).

The study was approved by the Local Ethics Committee of Muğla Sıtkı Koçman University. Written informed consent was obtained from all patients.

Sample size

The study was designed to target a large, representative number of AF patients in Turkey. The prevalence of AF in Turkey has been estimated to be 1.25% (15); the AF population size was estimated to be 971,199 based on Turkish Statistical Institute 2014 data (16). Assuming a response rate of 80% with a 1% margin of error and 95% confidence interval, the required sample size was calculated to be 6108; adding 25% to account for probable drop out resulted in a total sample size of 7635. These patients were enrolled from the seven regions of Turkey in proportion to the population of each region.

Statistical analysis

Continuous variables are summarized as median and interquartile range or mean \pm standard deviation (SD). Categorical variables are expressed as frequencies and percentages. Univariate analyses were performed for continuous variables, and the chi-square test was used for categorical variables. All analyses were performed using Statistical Package for Social Sciences software (SPSS 21, Chicago, Illinois). A p value of < 0.05 was considered to be statistically significant.

Results

Enrollment

The intention was to enroll a total of 7635 patients from 68 sites. However, 11 sites were unable to recruit patients due to a

heavy workload and were dropped from the study. From the remaining 57 sites, 6273 patients were enrolled from 29 provinces in Turkey with the contribution of 83 investigators. The mean age was 69.6±10.7 years, and 56% of the patients were females. The distribution of patients according to Turkey's seven regions was as follows: Marmara 1677 (26.7%), Central Anatolia 1024 (16.3%), Black Sea 907 (14.5%), Mediterranean 796 (12.7%), Aegean 745 (11.9%), East Anatolia 662 (10.6%), and Southeast Anatolia 462 (7.4%). Nearly 50% of the patients (45.1%) were recruited from tertiary hospitals, 43.6% were recruited from state hospitals, and 11.3% were recruited from private hospitals.

Antithrombotic therapy use

Overall OAC use was 72%, and 32% of the patients were receiving antiplatelet therapies. The percentages of patients according to their antithrombotic drug prescription were as

follows: NOAC alone 31%, VKA alone 27%, antiplatelet therapy alone 19%, OAC and antiplatelet therapy 13%, and no antithrombotic drug 8%. The baseline characteristics of the patients are presented in Table 1 according to their antithrombotic drug use. The most frequent comorbid diseases associated with antiplatelet drug therapy were CHD and CHF, and VKAs were preferred over NOACs in CHD or CHF patients.

Stroke risk factors

The most prevalent comorbid condition was hypertension (69%), and about 20% of the patients had at least one comorbid disease. The mean scores across the study population were 1.8±1.7 for CHADS₂, 3.3±1.6 for CHA₂DS₂-VASc (with 93% of the patients having a score of ≥1, not including those scoring 1 solely due to being females, and 87% had a score of ≥2), and 1.6±1.1 for HAS-BLED (with 80% of the patients having a score of ≤2).

Table 1. Demographic characteristics of the patients

Demographics	Overall (n=6273)	NOAC alone (n=1941)	VKA alone (n=1720)	Antiplatelet alone (n=1181)	OAC+Antiplatelet (n=818)	None (n=535)	P
Male, n (%)	2769 (44)	733 (38)	716 (42)	576 (49)	359 (44)	253 (47)	<0.001
Age, years	69.6±10.7	70.8±10.1	68.4±10.3	70.8±10.9	68.0±10.2	69.3±13.4	<0.001
Age, median (IQR)	70 (63–77)	72 (65–78)	69 (62–76)	72 (64–72)	69 (61–76)	71 (62–80)	<0.001
Smoker, n (%)	1023 (16)	242 (12)	235 (14)	259 (22)	177 (22)	98 (18)	<0.001
Alcohol use, n (%)	147 (2)	43 (2)	14 (1)	29 (2)	36 (4)	22 (4)	<0.001
Place of residence, Urban n (%)	4051 (65)	1347 (69)	1244 (72)	572 (48)	559 (68)	292 (55)	<0.001
Education, n (%)							<0.001
Illiterate	1860 (30)	491 (25)	439 (25)	489 (41)	184 (22)	232 (43)	
Primary	2267 (36)	622 (32)	745 (43)	429 (36)	276 (34)	171 (32)	
Secondary	802 (13)	281 (14)	240 (14)	107 (9)	126 (15)	44 (8)	
High	890 (14)	366 (19)	208 (12)	106 (9)	162 (20)	45 (8)	
University	350 (6)	156 (8)	53 (3)	39 (3)	65 (8)	37 (7)	
AF type, n (%)							<0.001
Persistent/permanent	5066 (81)	1637 (84)	1426 (83)	887 (75)	677 (83)	375 (70)	
Paroxysmal	859 (14)	234 (12)	194 (11)	236 (20)	110 (13)	77 (14)	
First attack	290 (5)	42 (2)	89 (5)	47 (4)	30 (4)	78 (15)	
Hypertension, n (%)	4305 (69)	1334 (69)	1165 (68)	861 (73)	566 (69)	320 (60)	<0.001
CHD, n (%)	1828 (29)	312 (16)	383 (22)	546 (46)	507 (62)	61 (11)	<0.001
COPD, n (%)	1448 (23)	362 (19)	356 (21)	391 (33)	182 (22)	133 (25)	<0.001
DM, n (%)	1389 (22)	419 (22)	371 (22)	265 (22)	230 (28)	88 (16)	<0.001
CHF, n (%)	1386 (22)	295 (15)	345 (20)	349 (30)	286 (35)	89 (17)	<0.001
Stroke/TIA, n (%)	845 (13.5)	300 (15)	231 (13)	132 (11)	139 (17)	36 (7)	<0.001
CHADS ₂	1.8±1.7	1.6±1.2	1.6±1.2	2.0±1.5	1.9±1.3	1.5±1.2	<0.001
CHA ₂ DS ₂ -VASc	3.3±1.6	3.1±1.6	3.1±1.6	3.5±1.6	3.7±1.7	2.8±1.4	<0.001
HAS-BLED	1.6±1.1	1.5±1.1	1.5±1.0	2.0 1.0	2.2±1.3	1.3±0.9	<0.001

Values are given as mean±standard deviation (SD) unless otherwise specified. AF - atrial fibrillation; CHADS₂ - congestive heart failure or left ventricular dysfunction, hypertension, age ≥65 years, diabetes, thromboembolism or stroke history; CHA₂DS₂-VASc - congestive heart failure or left ventricular dysfunction, hypertension, age ≥75 years, diabetes, thromboembolism or stroke history, vascular disease, age 65–74 years, female sex; CHD - coronary heart disease; CHF - congestive heart failure; COPD - chronic obstructive pulmonary disease; DM - diabetes mellitus; HAS-BLED - hypertension, renal or liver failure, stroke history, bleeding history, labile international normalized ratio, age >65 years, drugs, or alcohol, IQR - interquartile range; NOAC - non-vitamin K antagonist oral anticoagulant; TIA - transient ischemic attack; VKA - vitamin K antagonist

Antithrombotic therapy use related to the CHA₂DS₂-VASc and HAS-BLED scores

The overall antithrombotic therapy use was 91%. Antithrombotic therapy was provided for 88% of the patients with a CHA₂DS₂-VASc score of 0, with 72% of these on OAC therapy. Of the patients with a score of ≥ 1 for CHA₂DS₂-VASc, 91% were on antithrombotic therapy, with 72% of these on OAC therapy. Of the patients with a score of < 3 for HAS-BLED, 90% were on antithrombotic therapy, with 74% of these on OAC therapy. Notably, 95% of the patients with a HAS-BLED score of ≥ 3 were on antithrombotic therapy, with 67% of these on OAC therapy. Figure 1 illustrates OAC use versus CHA₂DS₂-VASc and HAS-BLED risk scores.

Antithrombotic therapy and rate/rhythm control strategies

The most frequently used NOAC was dabigatran (18%), followed by rivaroxaban (15%) and apixaban (4%). The majority of antiplatelet therapy consisted of acetylsalicylic acid (26%), with only a minority of patients (4%) on other antiplatelet drugs. Most patients (88%) were on at least one rate/rhythm drug. The details of the patients' medication are summarized in Table 2. Majority of the patients (79%) were on a rate control strategy, with only 9% on a rhythm control strategy. The most frequently used rate control therapy was beta-blockers (63%), with amiodarone (5%) preferred for rhythm control.

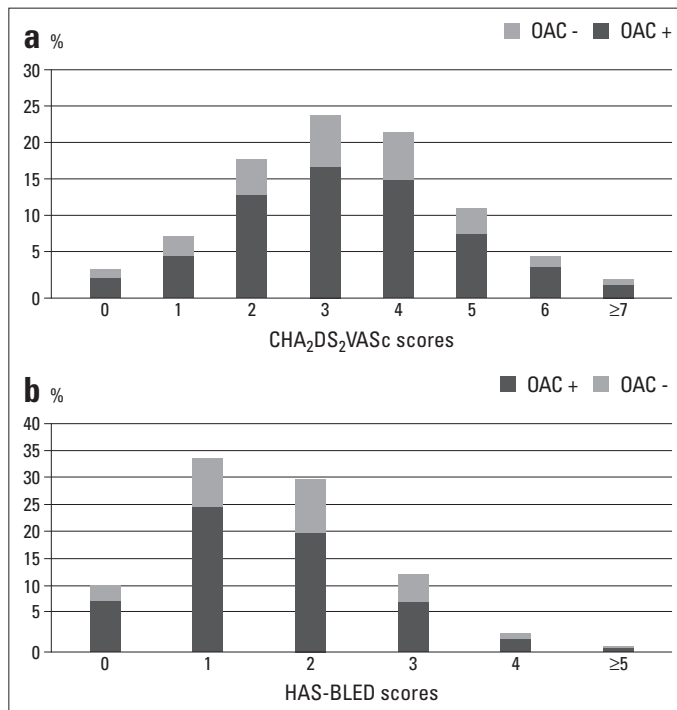


Figure 1. (a) Oral anticoagulant use according to the patients' CHA₂DS₂-VASc scores (which take into account congestive heart failure, hypertension, age ≥ 75 or 65–74 years, diabetes, stroke history, vascular disease, and sex). (b) Oral anticoagulant use according to the patients' HAS-BLED scores (which take into account hypertension, renal/liver failure, stroke history, bleeding history, labile international normalized ratio, age > 65 years, drugs predisposing to bleeding, and alcohol use). Values are given as percentages

Comparison of patient characteristics with previous studies

Table 3 presents a comparison of patient characteristics with those of patients enrolled in previous RCTs and observational clinical trials. The baseline characteristics of our study population were in accordance with those in other observational studies. However, the CHA₂DS₂-VASc and HAS-BLED scores and the prevalence of comorbid diseases associated with stroke risk were higher in patients enrolled in RCTs.

Discussion

The RAMSES study is the largest study to date of Turkish NVAF patients and is one of the largest in the world. It has demonstrated the widespread adoption of NOACs in the daily clinical practice of cardiologists. The overall antithrombotic therapy use was 91% and 72% of the patients received OAC therapy. However, the overuse of OAC therapy is a problem; we found that 72% of the patients with a CHA₂DS₂-VASc score of 0 were on OAC therapy. The overuse of antiplatelet therapy was also common, especially in patients with CHD or heart failure (with or without anticoagulation). Anticoagulant therapy was used less often in patients with lower education levels and in those who lived in rural areas, with antiplatelet drugs the preferred antithrombotic therapy for these patients.

Table 2. Antithrombotic and antiarrhythmic therapies of the patients

Medication history	N (%)
Anticoagulant therapy	4513 (72)
Non-vitamin K antagonist oral anticoagulants	2340 (37)
Dabigatran	1148 (18)
Rivaroxaban	942 (15)
Apixaban	250 (4)
Vitamin K antagonist	2173 (35)
Antiplatelet therapy	2010 (32)
Acetylsalicylic acid	1624 (26)
Clopidogrel, prasugrel, ticagrelor	231 (4)
Dual antiplatelet	155 (2)
VKA + dual antiplatelet	19 (0.3)
NOAC + dual antiplatelet	20 (0.3)
Drugs for rate/rhythm control	5429 (88.4)
Beta blocker	3889 (63.3)
Non-dihydropyridine calcium channel blocker	1451 (23.6)
Digoxin	1259 (20.5)
Amiodarone	295 (4.8)
Propafenone	174 (2.8)
Sotalol	56 (0.9)
Other	292 (4.8)

Values are given as percentages

Table 3. Comparison of baseline characteristics of patients enrolled in RAMSES with randomized controlled trials and observational studies

N (%)	Randomized controlled trials			Observational trials					
	RE-LY (n=18113)	ROCKET-AF (n=14264)	ARISTOTLE (n=18201)	GLORIA-AF (n=10675)	GARFIELD (n=10614)	ORBIT-AF (n=9484)	EORP-AF (n=3049)	AFTER (n=1745)	RAMSES (n=6273)
Age±SD, year	71.5±8.7	–	–	–	70.2±11.2	–	68.8	69.1±11.2	69.7±10.7
Age, median (IQR), year	–	73 (65–78)	70 (63–76)	71 (64–78)	–	75 (67–82)	–	–	70 (63–77)
Male	11514 (63.6)	8601 (60.3)	11785 (65.2)	5813 (54.4)	6034 (56.8)	–	–	761 (43.6)	2769 (44.0)
Previous stroke or TIA	3623 (20.0)	7811 (54.8)	3538 (19.4)	999 (9.4)	1528 (14.4)	–	–	266 (15.2)	845 (13.5)
Heart failure	5793 (32.0)	8908 (62.4)	5498 (30.2)	2530 (23.7)	2229 (21.0)	–	1382 (47.5)	537 (30.7)	1386 (22.0)
Diabetes mellitus	4221 (23.3)	5695 (39.9)	4547 (25.0)	2454 (23.0)	2330 (22.0)	–	–	416 (23.8)	1389 (22.0)
Hypertension	14283 (78.8)	12910 (90.5)	15916 (87.4)	7993 (74.9)	8249 (77.8)	–	–	1274 (73.0)	4305 (69.0)
CHADS ₂	2.1±1.1	3.5±0.9	2.1±1.1	1.9±1.1	1.9±1.2	2.3±1.3	1.9±1.3	–	1.8±1.7
CHA ₂ DS ₂ VASc	–	–	–	3.2±1.5	3.2±1.6	–	3.2±1.8	3.5±1.7	3.3±1.6
OAC	VKA:6022 D110:6015 D150:6076	VKA: 7133 R: 7131 –	VKA: 9081 A: 9120 –	VKA:3449 D:3439 R:1282, A:369	VKA:5925 NOAC:475 –	–	–	–	VKA: 2173 D: 1148 R: 942, A:250
OAC, %	VKA: 33 D110: 33 D150: 33	VKA: 50 R: 50 –	VKA: 50 A: 50 –	VKA: 32 D: 32 R: 12, A:3	VKA: 56 NOAC: 4 –	VKA: 72 D: 4.8 –	VKA: 71 D: 7 R: 2	VKA: 40 – –	VKA:34 D: 18 R: 15, A: 4
No OAC, %	–	–	–	2136 (20%)	4214 (40%)	23 %	20 %	60 %	1716 (27%)

Values are given as mean±standard deviation (SD) or number (percentage). AFTER - Atrial fibrillation in Turkey: Epidemiologic registry, A-apixaban; ARISTOTLE - apixaban for reduction in stroke and other thromboembolic events in atrial fibrillation; CHADS₂ - congestive heart failure or left ventricular dysfunction, hypertension, age ≥65 years, diabetes, thromboembolism or stroke history; CHA₂DS₂VASc - congestive heart failure or left ventricular dysfunction, hypertension, age ≥75 years, diabetes, thromboembolism or stroke history, vascular disease, age 65–74 years, female sex; D - dabigatran; EORP-AF - euroobservational research programme on atrial fibrillation; GARFIELD - global anticoagulant registry in the field; GLORIA-AF - global registry on long-term oral antithrombotic treatment in patients with atrial fibrillation; IQR - interquartile range; NOAC - non-vitamin K antagonist oral anticoagulant; OAC - oral anticoagulant; ORBIT-AF - outcomes registry for better informed treatment of atrial fibrillation; RAMSES - ReAl-life Multicenter Survey Evaluating Stroke Prevention Strategies in Turkey; RE-LY - randomized evaluation of long-term anticoagulation therapy; R - rivaroxaban; ROCKET-AF - rivaroxaban once daily oral direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation; TIA - transient ischemic attack; VKA-vitamin K antagonist

The limitations of warfarin have restricted the use of OAC therapy, especially in developing countries (17). The situation is complex in Turkey. OAC use for AF was found to be 30.1% in a single-center study, whereas a tertiary center study showed 67.3% of AF patients to be on OAC therapy (18, 19). However, a multicenter study found that 40% of NVAF patients were on warfarin, 43% were on antiplatelet therapy, and 17% were not receiving any antithrombotic therapy for stroke prophylaxis (12). The main reason for patients not being on OAC therapy was physicians' neglect (7). These previous studies have reported that the limitations of warfarin therapy may have prevented physicians in Turkey from prescribing OAC therapy. Global registries provide a better profile of OAC use in AF patients. The rate of prescribing OACs was 60% in the GARFIELD study, 60.9% in the Euro Heart Survey, and 71.4% in the Central Registry of the Ger-

man Competence Network on Atrial Fibrillation (8, 11, 20). It is notable that recent registries have shown an increase in the rate of patients on OAC therapy, with an overall OAC use of 80% (10, 21, 22). These registries have been established subsequent to the publication of the 2012 ESC guidelines for the management of AF, which emphasized OAC therapy for stroke prevention in AF and restricted antiplatelet therapy (1). Our study showed that 72% of the NVAF patients were on OAC therapy (37% NOAC and 35% VKA), 19% were on antiplatelet therapy, and 9% were not receiving any antithrombotic therapy. These results could partly be attributed to the ESC guidelines. Another reason for the changing of OAC prescription patterns in NVAF patients in Turkey could be the availability of NOACs as an alternative to VKA therapy.

The introduction of NOACs to daily clinical practice has provided physicians with a good opportunity for preventing AF-

related strokes, and the present study showed that NOACs are preferred over VKAs for stroke prophylaxis in NVAF patients. VKAs have many limitations, including the need for frequent INR monitoring, interactions with foods and drugs, slow onset and offset of action, and variability in their anticoagulation effect. In a recent study, we showed that the inappropriate use of warfarin might be up to 83% and that the mean time in therapeutic range (TTR) was 40.5% (23). Another Turkish study showed the mean TTR of NVAF patients to be 40.3% (24). The results of these national studies suggest that the poor quality of anticoagulation with warfarin is a reason for the preference of NOACs over VKAs in Turkey. Another reason for the wide use of NOACs could be the reimbursement to patients of the costs of NOACs in our country; dabigatran was subject to reimbursement from May 2013, rivaroxaban from October 2013, and apixaban from July 2014. In parallel, dabigatran was the most frequently used NOAC, followed by rivaroxaban and apixaban in our study.

According to their CHA₂DS₂-VASc scores, approximately nine of ten NVAF patients needed OAC therapy in the present study, which was consistent with previous studies (25). Although there has been an increase in OAC use in Turkey compared to that reported in previous national studies, a considerable percentage of patients (28%) who needed anticoagulation (CHA₂DS₂-VASc score ≥ 1) still received no OAC therapy (7). The patients who were only on antiplatelet therapy had higher CHA₂DS₂-VASc and HAS-BLED scores. Concerns about bleeding may have prevented physicians from prescribing OACs for patients with higher HAS-BLED scores, possibly resulting in the overprescription of antiplatelet agents. However, current data show that the risk of major bleeding does not differ between aspirin and warfarin (26). Antiplatelet therapy was used with or without anticoagulant therapy, in patients who had CHD or CHF in particular. Although antiplatelet therapy is one of the main therapeutic interventions in CHD patients, OAC monotherapy is recommended for patients with AF and stable coronary artery disease (1, 27). Triple or dual therapies may be chosen only for patients undergoing revascularization or those who experienced an acute coronary syndrome. The present study showed that the patients who were on anticoagulant and antiplatelet therapy had the greatest risk for both stroke and bleeding risk as assessed by the CHA₂DS₂-VASc and HAS-BLED scores. The overuse of antithrombotic therapies increases the risk of major bleeding without a reduction in thromboembolism (28). Therefore, the need for combination therapy should be regularly evaluated based on risk-benefit considerations. A further issue is the overuse of OAC therapies in AF patients with a low stroke risk. Observational studies have reported an overuse rate of OAC therapy of approximately 50% in AF patients with low stroke risk (8, 20, 22). We found that 72% of the AF patients who were at a low stroke risk were on OAC therapy. However, most patients with a CHA₂DS₂-VASc score of 0 were enrolled in tertiary hospitals, and these patients may have been referred to those hospitals for complex procedures such as cardioversion or AF ablation.

Most of our patients lived in urban areas. One-third were illiterate, and only 6% were university graduates. An association relating lower education levels, socioeconomic status, and AF incidence has been shown (29). Low socioeconomic status was also a risk factor for hemorrhage in AF patients who were on VKA therapy (30). In addition, illiteracy and older age were associated with poor knowledge of OAC therapy in another study (31). In contrast, it has also been reported that adherence to warfarin treatment was poor in educated patients (32). Physicians' concerns regarding adherence to OAC therapy among patients with lower education and socioeconomic status and the fear of hemorrhagic complications may have led to a lesser rate of prescribing OACs for these patients. However, lower education and socioeconomic status should not be a reason for a patient not being given OAC therapy.

We showed that hypertension was the most common comorbid situation in NVAF patients, followed by CHD, chronic obstructive pulmonary disease, heart failure, and diabetes mellitus. These findings are consistent with those in previous studies (7, 8, 20). Our study enrolled more female patients than male patients, unlike most other studies that mostly enrolled male patients. This may be due to the higher incidence of AF in Turkish female patients (15). The mean age of NVAF patients was approximately 70 years, consistent with previous RCTs and observational studies. RCTs generally enrolled patients with a greater number of stroke-related comorbid diseases and higher CHADS₂ scores. Unlike RCTs, observational studies try to capture a broad spectrum of the disease. The comorbid diseases were similar across observational studies, except for the EORP-AF study, in which nearly 50% of the patients had heart failure (22). The results of the present study showed an increase in OAC use in Turkey, with a rate comparable to that found in large multicenter registries. The most preferred OAC was VKA in ORBIT-AF and GARFIELD trials, whereas NOAC use was more common in the more recent GLORIA-AF trial (21, 33, 34). Our study also showed NOACs were preferred over VKAs in Turkish NVAF patients.

Study limitations

Our study was a snapshot of patient characteristics, and therefore it could not provide information regarding the course of the disease, stroke rates, and mortality. However, it provides useful, real-life data regarding NVAF patients seen in daily clinical practice. The study was conducted in outpatient cardiology clinics, and this may have limited the coverage of all NVAF patients; however, participating institutions were widely distributed geographically across Turkey—both the smaller and main cities of Turkey were represented according to their populations. Another limitation of our study was that it did not provide any information regarding the prevalence or incidence of the disease and no prospective data of VKA anticoagulation quality.

Conclusion

Our findings showed that the awareness of stroke prevention strategies for NVAF has increased in Turkey and that more than two-thirds of NVAF patients were on OAC therapy. However, the rate of antiplatelet use was still high among NVAF patients. The findings also showed that NOACs are preferred over VKAs for anticoagulation in a representative clinical population of NVAF patients.

Appendix (*numbers indicate cities)

Collaborators: Sinan İnci¹, Bernas Altıntaş², Sedat Kalkan³, Fatma Özpamuk Karadeniz⁴, Ahmet İlker Tekkesin⁵, Yasin Çakallı⁶, Ceyhan Türkan⁵, Mehmet Hamidi⁷, Vahit Demir⁸, Mustafa Ozan Gürsoy⁹, Müjgan Tek Öztürk¹⁰, Gökhan Aksan¹¹, Sabri Seyis¹², Mehmet Ballı¹³, Mehmet Hayri Alıcı¹⁴, Serdar Bozyel¹⁵, Feyza Çalık¹⁶, Oğuz Karaca¹⁷, Füsün Helvacı¹¹, Kadriye Akay¹⁸, Yiğit Çanga¹⁹, Savaş Çelebi²⁰, Emine Altuntaş²¹, Mehmet Aytürk¹⁰, Hacı Murat Güneş¹⁷, Tahir Bezgin²², Aytekin Aksakal²³, Beytullah Çakal¹⁷, Ayşe Çolak²⁴, Özgür Kaplan²⁵, Adem Tatlısu²⁶, Gökhan Gözübüyük²⁵, Selami Demirelli²⁷, Adnan Kaya²⁸, İbrahim Rencüzoğulları²⁹, Zübeyde Bayram¹⁹, Zeki Şimşek¹⁹, Murat Civan³⁰, Ulaankhu Batghareli³¹, Ali Ekber Ata³², Gökhan Göl³³, Gurbet Özge Mert³⁴, Kadir Uğur Mert³⁴, Aleks Değirmencioğlu³⁵, Özkan Candan³⁶, Özlem Özcan Çelebi³⁷, Cem Doğan²⁵, Fethi Yavuz³⁸, Şeref Ulucan³⁹, Arif Arısoy⁴⁰, Bingül Dilekçi Şahin²⁷, Emrah Ermiş²⁷, Serkan Gökaslan⁴¹, İdris Pektaş⁴², Aslı Tanındı⁴³, Kamuran Tekin⁴⁴, Kadriye Memic Sancar³⁴, Edip Güvenç Çekiç⁴⁵, Nesrin Filiz Başaran⁴⁵

The cities involved in the collaboration: ¹Aksaray, ²Diyarbakır, ³Balıkesir-Gönen, ⁴Şanlıurfa, ⁵İstanbul, ⁶İstanbul, ⁷Balıkesir, ⁸Yozgat, ⁹İzmir, ¹⁰Ankara, ¹¹İstanbul, ¹²Mersin, ¹³Mersin, ¹⁴Gaziantep, ¹⁵Kocaeli, ¹⁶Mersin, ¹⁷İstanbul, ¹⁸Kocaeli, ¹⁹İstanbul, ²⁰Ankara, ²¹Bingöl, ²²Kocaeli, ²³Samsun, ²⁴Mersin, ²⁵Malatya, ²⁶Sivas, ²⁷Erzurum, ²⁸Şanlıurfa, ²⁹Kars, ³⁰İstanbul, ³¹İstanbul, ³²Samsun, ³³İstanbul, ³⁴Muğla, ³⁵İstanbul, ³⁶Uşak, ³⁷Ankara, ³⁸Gaziantep, ³⁹Konya, ⁴⁰Tokat, ⁴¹İstanbul, ⁴²Mersin, ⁴³Ankara, ⁴⁴Batman, ⁴⁵Muğla

Conflict of interest: None declared.

Peer-review: Externally peer-reviewed.

References

1. Camm AJ, Lip GY, De Caterina R, Savelieva I, Atar D, Hohnloser SH, et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation. *Eur Heart J* 2012; 33: 2719-47.
2. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009; 361: 1139-51.
3. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011; 365: 883-91.
4. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011; 365: 981-92.
5. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2013; 369: 2093-104.
6. Lip GY, Al-Khatib SM, Cosio FG, Banerjee A, Savelieva I, Ruskin J, et al. Contemporary management of atrial fibrillation: what can clinical registries tell us about stroke prevention and current therapeutic approaches? *J Am Heart Assoc* 2014 Aug 27. Epub ahead of print.
7. Ertaş F, Kaya H, Kaya Z, Bulur S, Köse N, Gül M, et al. Epidemiology of atrial fibrillation in Turkey: preliminary results of the multicenter AFTER study. *Türk Kardiyol Dern Ars* 2013; 41: 99-104.
8. Nabauer M, Gerth A, Limbourg T, Schneider S, Oeff M, Kirchhof P, et al. The Registry of the German Competence NETwork on Atrial Fibrillation: patient characteristics and initial management. *Europace* 2009; 11: 423-34.
9. Huisman MV, Lip GY, Diener HC, Dubner SJ, Halperin JL, Ma CS, et al. Design and rationale of Global Registry on Long-Term Oral Antithrombotic Treatment in Patients with Atrial Fibrillation: a global registry program on long-term oral antithrombotic treatment in patients with atrial fibrillation. *Am Heart J* 2014; 167: 329-34.
10. Steinberg B, Blanco RG, Ollis D, Kim S, Holmes DN, Kowey PR, et al. Outcomes registry for better informed treatment of atrial fibrillation II: Rationale and design of the ORBIT-AF II registry. *Am Heart J* 2014; 168: 160-7.
11. Kakkar AK, Mueller I, Bassand JP, Fitzmaurice DA, Goldhaber SZ, Goto S, et al. International longitudinal registry of patients with atrial fibrillation at risk of stroke: Global Anticoagulant Registry in the FIELD (GARFIELD). *Am Heart J* 2012; 163: 13-9.
12. Kaya H, Ertaş F, Köroğlu B, Vatan B, Çağlıyan ÇE, Gedik S, et al. Predictors of anticoagulant treatment in patients with nonvalvular atrial fibrillation: results from atrial fibrillation in Turkey: epidemiologic registry. *Clin Appl Thromb Hemost* 2015; 21: 144-8.
13. Kılıçkiran Avcı B, Vatan B, Tok OO, Aidarova T, Şahinkuş S, Uygun T, et al. The trends in utilizing nonvitamin K antagonist oral anticoagulants in patients with nonvalvular atrial fibrillation: A real-life experience. *Clin Appl Thromb Hemost* 2015 Apr 15. Epub ahead of print.
14. Heidebuchel H, Verhamme P, Alings M, Antz M, Diener HC, Hacke W, et al. Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation. *Europace* 2015; 17: 1467-507.
15. Uyarel H, Onat A, Yüksel H, Can G, Ordu S, Dursunoğlu D. Incidence, prevalence, and mortality estimates for chronic atrial fibrillation in Turkish adults. *Türk Kardiyol Dern Ars* 2008; 36: 214-22.
16. TÜİK, Türkiye İstatistik Kurumu, Adrese Dayalı Nüfus Kayıt Sistemi Sonuçları, 2014 Jan;18616:1-2 <http://www.tuik.gov.tr/PreHaber-Bultenleri.do?id=18616>
17. Nguyen TN, Hilmer SN, Cumming RG. Review of epidemiology and management of atrial fibrillation in developing countries. *Int J Cardiol* 2013; 167: 2412-20.
18. Karacağlar E, Atar I, Yetiş B, Corut H, Ersoy B, Yılmaz K, et al. The frequency of embolic risk factors and adequacy of anti-embolic treatment in patients with atrial fibrillation: A single tertiary center experience. *Anadolu Kardiyol Derg* 2012; 12: 384-90.
19. Ertaş F, Duygu H, Acet H, Eren NK, Nazlı C, Ergene AO. Oral anticoagulant use in patients with atrial fibrillation. *Türk Kardiyol Dern*

- Ars 2009; 37: 161-7.
20. Nieuwlaet R, Capucci A, Lip GY, Olsson SB, Prins MH, Nieman FH, et al. Antithrombotic treatment in real-life atrial fibrillation patients: A report from the Euro Heart Survey on Atrial Fibrillation. *Eur Heart J* 2006; 27: 3018-26.
 21. Huisman MV, Rothman KJ, Paquette M, Teutsch C, Diener HC, Dubner SJ, et al. Antithrombotic Treatment Patterns in Patients with Newly Diagnosed Nonvalvular Atrial Fibrillation: The GLORIA-AF Registry, Phase II. *Am J Med* 2015; 128: 1306-13.
 22. Lip GY, Laroche C, Dan GA, Santini M, Kalarus Z, Rasmussen LH, et al. A prospective survey in European Society of Cardiology member countries of atrial fibrillation management: baseline results of Euro Observational Research Programme Atrial Fibrillation (EORP-AF) Pilot General Registry. *Europace* 2014; 16: 308-19.
 23. Başaran O, Filiz Başaran N, Çekiç EG, Altun I, Doğan V, Mert GO, et al. PRescriptiOn PAttERns of Oral Anticoagulants in Nonvalvular Atrial Fibrillation (PROPER study). *Clin Appl Thromb Hemost* 2015 Oct 30. Epub ahead of print.
 24. Türk UO, Tuncer E, Alioğlu E, Yüksel K, Pekel N, Özpelit E, et al. Evaluation of the impact of warfarin time in therapeutic range on outcomes of patients with atrial fibrillation in Turkey: Perspectives from the observational, prospective WATER Registry. *Cardiol J* 2015; 22: 567-75.
 25. Lip GY, Frison L, Halperin JL, Lane DA. Identifying patients at high risk for stroke despite anticoagulation: A comparison of contemporary stroke risk stratification schemes in an anticoagulated atrial fibrillation cohort. *Stroke* 2010; 41: 2731-8.
 26. Mant J, Hobbs FD, Fletcher K, Roalfe A, Fitzmaurice D, Lip GY, et al. Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomised controlled trial. *Lancet* 2007; 370: 493-503.
 27. Clappers N, Brouwer MA, Verheugt FW. Antiplatelet treatment for coronary heart disease. *Heart* 2007; 93: 258-65.
 28. Fisher M. Does the combination of warfarin and aspirin have a place in secondary stroke prevention? No. *Stroke* 2009; 40: 1944-5.
 29. Misialek JR, Rose KM, Everson-Rose SA, Soliman EZ, Clark CJ, Lopez FL, et al. Socioeconomic status and the incidence of atrial fibrillation in whites and blacks: the Atherosclerosis Risk in Communities (ARIC) study. *J Am Heart Assoc* 2014; Aug 20. Epub ahead of print.
 30. Cressman AM, Macdonald EM, Yao Z, Austin PC, Gomes T, Paterson JM, et al. Socioeconomic status and risk of hemorrhage during warfarin therapy for atrial fibrillation: A population-based study. *Am Heart J* 2015; 170: 133-40.
 31. Joshua JK, Kakkar N. Lacunae in patient knowledge about oral anticoagulant treatment: results of a questionnaire survey. *Indian J Hematol Blood Transfus* 2015; 31: 275-80.
 32. Platt AB, Localio AR, Brensinger CM, Cruess DG, Christie JD, Gross R, et al. Risk factors for nonadherence to warfarin: results from the IN-RANGE study. *Pharmacoepidemiol Drug Saf* 2008; 17: 853-60.
 33. Kakkar AK, Mueller I, Bassand JP, Fitzmaurice DA, Goldhaber SZ, Goto S, et al. Risk profiles and antithrombotic treatment of patients newly diagnosed with atrial fibrillation at risk of stroke: perspectives from the international, observational, prospective GARFIELD registry. *PLoS One* 2013; 8: e63479.
 34. Steinberg BA, Kim S, Fonarow GC, Thomas L, Ansell J, Kowey PR, et al. Drivers of hospitalization for patients with atrial fibrillation: Results from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF). *Am Heart J* 2014; 167: 735-42.