Analysis of geographical variations in the epidemiology and management of non-valvular atrial fibrillation: results from the RAMSES registry

*Volkan Doğan[1], Özcan Başaran[1], Murat Biteker[1], Fatma Özpamuk Karadeniz[2], Ahmet İlker Tekkesin[3], Yasin Çakıllı[4], Ceyhan Türkkan[3], Mehmet Hamidi[5], Vahit Demir[6], Mustafa Ozan Gürsoy[7], Müjgan Tek Öztürk[8], Gökhan Aksan[9], Sabri Seyis[10], Mehmet Ballı[11], Mehmet Hayri Alıcı[12], Serdar Bozyel[13], Cevat Kırma[14] and Collaborators**

[1]Department of Cardiology, Faculty of Medicine, Muğla Sıtkı Kocman University; Muğla-*Turkey*, [2]Department of Cardiology, Şanlıurfa Balıklıgöl State Hospital; Şanlıurfa- *Turkey*, [3]Department of Cardiology, Siyami Ersek Heart Education and Research Hospital; İstanbul- *Turkey*, [4]Department of Cardiology, Tuzla State Hospital; İstanbul-*Turkey*, [5]Department of Cardiology, Bandırma State Hospital; Balıkesir-*Turkey*, [6]Department of Cardiology, Yozgat State Hospital; Yozgat-*Turkey*, [7]Department of Cardiology, Gaziemir State Hospital; İzmir-*Turkey* [8]Department of Cardiology, Ankara Keçiören Education and Research Hospital; Ankara-*Turkey*, [9]Department of Cardiology, Şişli Hamidiye Etfal Education and Research Hospital; İstanbul- *Turkey*, [10]Department of Cardiology, Mersin Private Doğuş Hospital; Mersin-*Turkey*, [11]Department of Cardiology, Mersin Toros State Hospital; Mersin-*Turkey*, [12]Department of Cardiology, Gaziantep 25 Aralık State Hospital; Gaziantep-*Turkey*, [13]Department of Cardiology, Kocaeli Derince Education and Research Hospital; Kocaeli-*Turkey* [14]Department of Cardiology, Kartal Koşuyolu Heart Education and Research Hospital; İstanbul-*Turkey*

Abstract

Objective: This study aimed to determine the differences in terms of demographic characteristics and preferred stroke prevention strategies for patients with non-valvular atrial fibrillation living in seven geographical regions of Turkey.

Methods: In total, 6273 patients were enrolled to this prospective, observational RAMSES study. The patients were divided into seven groups based on the geographical region of residence.

Results: In terms of the geographical distribution of the overall Turkish population, the highest number of patients were enrolled from Marmara (1677, 26.7%). All demographic characteristics were significantly different among regions. Preferred oral anticoagulants (OACs) also differed between geographical regions; non-vitamin K OACs were preceded by warfarin in East Anatolia, Aegean, Southeast Anatolia, and Black Sea. Nearly one-third of the patients (28%) did not receive any OAC therapy. However, the number of patients not receiving any OAC therapy was higher in Southeast Anatolia (51.1%) and East Anatolia (46.8%) compared with other geographical regions of Turkey. Inappropriate use of OACs was also more common in East and Southeast Anatolia.

Conclusion: This study was the first to show that the demographic differences among the geographical regions may result in different preferences of stroke prevention strategies in Turkey. OACs are still under- or inappropriately utilized, particularly in the eastern provinces of Turkey. *(Anatol J Cardiol 2017; 18: 273-80)*

Keywords: epidemiology, chronic disease, anticoagulant therapy

Introduction

Atrial fibrillation (AF) is the most common cardiac rhythm disorder and is associated with an elevated risk of stroke, thromboembolism, and mortality (1). AF can be classified as valvular or non-valvular, the former typically resulting from mitral valve stenosis or valvular prosthesis.

Non-valvular AF (NVAF) is associated with a six-fold increase in the risk of stroke and accounts for 20%–25% of ischemic stroke events among older patients (1). With the aging of the population, the burden of NVAF is expected to double in the near future and present with important public health implications (1, 2). In patients with NVAF, the risk of thromboembolism increases with risk factors, such as old age, female sex, vas-

Address for correspondence: Dr. Volkan Doğan, Muğla Sıtkı Koçman Üniversitesi Tıp Fakültesi Orhaniye Mah. Haluk Özsoy Cad., 48000/Muğla-*Türkiye*
Phone: +90 252 214 13 26 E-mail: drvolkandogan@hotmail.com

Accepted Date: 23.06.2017 **Available Online Date:** 11.08.2017

DOI:10.14744/AnatolJCardiol.2017.7709

Anatol J Cardiol 2017; 18: 273-80
DOI:10.14744/AnatolJCardiol.2017.7709

cular disease, diabetes, hypertension, heart failure, or a prior history of stroke (2). Vitamin K antagonists (VKAs) have been the gold standard oral anticoagulant (OAC) for the prevention of stroke and thromboembolism in patients with AF since the discovery of warfarin in 1941. Identification of patients with NVAF who will benefit from anticoagulant therapy is a significant clinical challenge. The congestive heart failure or left ventricular dysfunction, hypertension, age ≥75 years, diabetes, prior thromboembolism or stroke, vascular disease, age 65–74 years, and sex (CHA_2DS_2VASc) score is a validated stroke for risk estimation in patients with NVAF, and those with scores ≥1 should be considered eligible for anticoagulant therapy unless the bleeding risk is prohibitive (3). As a result, current clinical guidelines recommend the use of OAC therapy, either VKA or non-VKA OAC (NOAC), for all patients with AF, except for those who are at a substantially low risk (patients aged <65 years, without any risk factors for stroke) (1). Despite clear guidelines on anticoagulant therapy (1), real-world analyses showed that most patients with NVAF are either inadequately treated with antiplatelets or do not receive any treatment at all (4, 5). Furthermore, some low-risk patients are overtreated with VKAs or NOAC (6, 7).

The First Geography Congress in Turkey, held in Ankara in 1941, divided Turkey into seven separate regions based on climate, human habitat, agricultural diversity, and topography. Such variations in these factors may contribute to regional differences in the prevalence and management of chronic diseases (8). The four western regions of Turkey, Marmara, Aegean, Central Anatolia, and Mediterranean, are the four most socioeconomically developed regions of the country. On the other hand, the three eastern regions, Black Sea, Eastern Anatolia, and Southeastern Anatolia, constitute the three least socioeconomically developed regions. These regions considerably differ in terms of demographic characteristics, educational levels, employment rates, level of welfare, and economic structure (9, 10). Such pronounced geographical differences in living conditions are likely to be reflected in the differences observed in the population's health status. The Burden of Disease Study in 2005 has suggested that the west, middle, north, and south regions followed patterns that were similar to European countries, while the disease and mortality patterns in the east were similar to those of developing countries (11).

There are no large-scale studies from Turkey on the incidence, prevalence, and mortality of AF, but the Turkish Adult Risk Factor Study, a cross-sectional prospective study of 3450 adults, found a prevalence of AF of 1.25% and an incidence of 1.35 per 1000 person-years (12). Although epidemiological characteristics and treatment modalities of NVAF have never been investigated before, they may vary based on the geographical regions of Turkey. The aim of our study was to demonstrate the epidemiological characteristics and stroke prevention strategies for NVAF in all regions of Turkey and determine any potential differences between these regions.

Methods

Study design and data collection

The design of the RAMSES study (ClinicalTrials.gov identifier NCT02344901) has been previously reported (13). Briefly, the RAMSES study was conducted as a large, national, multi-center, and cross-sectional registry. We included all consecutive patients aged ≥18 years who were admitted to a participating hospital with a confirmed diagnosis of NVAF.

To ensure adequate geographical diversity, the number of patients enrolled from each region was proportional to the population of the relevant region. In order to represent all patients treated under different healthcare settings, the study centers included were state, university, educational and research, and private hospitals.

Patients were enrolled to the RAMSES study between February 15, 2015 and May 20, 2015. Eighty-three investigators from 57 centers located in 29 cities of seven geographical regions participated in the study. The included investigators were employed in outpatient clinics of cardiology departments.

Patients with mechanical heart valves or mitral stenosis were excluded from the study. Clinical background information, including underlying diseases, medications, and laboratory data, were recorded for all patients. In addition, clinical and laboratory components of various risk score measures for stroke and bleeding [CHA_2DS_2VASc and hypertension, renal or liver failure, stroke history, bleeding history, labile international normalized ratio, age >65 years, and drug or alcohol abuse (HAS-BLED) scores, respectively] were collected. Patients' ongoing pharmacological treatment for stroke prevention and antiarrhythmic drug therapies were recorded. International normalized ratio (INR) values and creatinine levels were also recorded. For patients receiving the VKA therapy, time in therapeutic range (TTR) was calculated by the conventional method: in-range (2–3) INR values divided by all INR values of a patient.

Patients were classified into low, intermediate, and high stroke risk groups according to their CHA_2DS_2VASc scores. We considered patients with score 0 to have a low risk of stroke, those with score 1 to have an intermediate risk, and those with score ≥2 to have a high risk. OAC therapy under-utilization was defined and estimated in patients who had CHA_2DS_2VASc score ≥1. Renal function was estimated by creatinine clearance value calculated using the Cockroft–Gault formula. Inappropriate use of OACs was evaluated according to the current guidelines (1). Major bleeding was defined based on the criteria of the International Society on Thrombosis and Haemostasis, and minor bleeding was defined as having a non-major bleeding (14). The present study was approved by the local Ethics Committees of all participating centers. Written informed consent forms were obtained from all patients.

Patients were classified into three clinical sub-types of AF: paroxysmal, persistent, or permanent, according to the physician's perception of AF at the time of enrollment. The definitions

of AF sub-types were as follows: paroxysmal AF, persistent AF, or permanent AF (1).

Outcomes of major interest

Guideline-based use of anticoagulant therapy in eligible patients and the reason for not receiving OAC therapy were analyzed. The appropriateness of stroke prevention strategies in patients with NVAF was evaluated. CHA_2DS_2VASc and HAS-BLED scores were assessed. A special consideration was given to the differences in demographics, clinical history, medications, and appropriateness of stroke prevention strategies among seven regions of Turkey in this sub-study of the RAMSES registry. Definition of guideline adherence in the use of OACs was based on the recent AF guidelines of the European Society of Cardiology (1).

Treatment was considered to be adherent to guidelines if patients with CHA_2DS_2VASc score 0 or female sex with score 1 received no treatment and if OAC therapy was initiated in patients with CHA_2DS_2VASc score >0.

Undertreatment was defined as either receiving no treatment in the presence of risk factors or receiving antiplatelet therapy while the guidelines recommend the use of OAC.

Overtreatment was defined as patients with CHA_2DS_2VASc score 0 receiving an antithrombotic therapy.

Turkey's healthcare system

Turkey's healthcare system consists of a mixture of public and private health services. Turkey provides national healthcare under the National Health Insurance system. All residents registered with the Social Security Institution under this system can receive medical care free of charge in hospitals contracted to this institution.

Statistical analyses

Continuous variables were presented as median and interquartile range or mean±standard deviation. Normally distributed variables were analyzed using ANOVA, and non-normally distributed variables were analyzed using the Kruskal–Wallis test.

Categorical variables were presented as frequencies and percentages. Univariate analysis was performed for continuous variables, was used ANOVA test and chi-square tests were used for categorical variables. A p value of <0.05 was considered significant. Comparisons between the groups in Tables 1 and 3 were performed using the chi-square and ANOVA tests. All analyses were performed using Statistical Package for Social Sciences software (SPSS 21, Chicago, Illinois, USA).

Results

Study population

In total, 6273 patients were included in the RAMSES study. Patient distribution according to 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%) (Fig. 1). Approximately 45.1% of the patients were enrolled from tertiary hospitals, 43.6% from state hospitals, and 11.3% from private hospitals.

The mean age of the study population was 69.6±10.7 years, and 56% of the patients were females. AF was paroxysmal in 14% and persistent or permanent in 81% of the patients. Major concomitant diseases were hypertension (69%), heart failure (22%), diabetes (22%), stroke (13.5%), and coronary artery disease (29%).

Regional differences in demographic characteristics

The baseline characteristics of the patients among the seven regions of Turkey are listed in Table 1. Patients living in the Aegean region of Anatolia were older than those living in the remaining six regions. East and Southeast Anatolia were the least developed regions of Turkey, and the highest rate of illiteracy was noted in Southeast Anatolia (72.9%). Smoking status and prevalence of comorbidities including hypertension, chronic obstructive lung disease, heart failure, diabetes, stroke, and coronary artery disease also varied among regions. Prevalence of sustained AF (persistent or permanent) was higher than paroxysmal AF in all regions. The mean CHA_2DS_2VASc and HAS-BLED scores of the study population were 3.3±1.6 and 1.6±1.1, respectively. The lowest CHA_2DS_2VASc score was seen in the Black Sea region (3.1±1.6), and the lowest HAS-BLED score was seen in Central Anatolia (1.3±1.1).

Regional differences in stroke prevention strategies

The overall OAC use was 72%, and antiplatelet therapies were prescribed to 32% of patients. The percentages of patients prescribed antithrombotic drugs were as follows: warfarin, 35%; NOAC, 37%; and antiplatelet without OAC, 19%. Approximately 9% of patients were not prescribed antithrombotic drugs. The details of the medications used by the patients are summarized in Table 2. Use of NOAC preceded warfarin in East Anatolia, Aegean, Southeast Anatolia, and Black Sea. Dabigatran was the preferred NOAC in Mediterranean, Aegean, Southeast Anatolia, Central Anatolia, and Black Sea, whereas rivaroxaban was prescribed more than the other NOACs in East Anatolia and Marmara.

Regional differences in guideline-based use and quality of OAC therapy

Warfarin was prescribed to <20% of patients in East Anatolia, Southeast Anatolia, and Black Sea. In total, 2173 patients were on warfarin, and the mean TTR was 853.61%±25.4%. The quality of anticoagulation with VKA greatly differed among the seven regions, with the highest TTR noted in Black Sea and the lowest in Aegean. The distribution of the mean TTR values among the seven regions is given in Figure 2. Figure 3 shows the use of antithrombotic drugs according to the stroke risk groups. It was noted that most of the patients with low risk

Anatol J Cardiol 2017; 18: 273-80 DOI:10.14744/AnatolJCardiol.2017.7709

Table 1. Baseline characteristics of the patients according to the geographical regions

	Overall 6273	Mediterranean 796 (12.7%)	East Anatolia 662 (10.6%)	Aegean 745 (11.9%)	Southeast Anatolia 462 (7.4%)	Central Anatolia 1024 (16.3%)	Black Sea 907 (14.5%)	Marmara 1677 (26.7%)	*P*
Age, years	69.6±10.74	70.9±10.43	70.8±9.36	72.2±10.44	70±10.59	68.5±10	68.2±10.34	68.9±11.78	0.001
Male	2769 (44.1)	356 (44.7)	326 (49.2)	320 (43)	187 (40.5)	385 (37.6)	408 (45)	787 (46.9)	0.001
Smoking	1023 (16.3)	109 (13.7)	146 (22.1)	79 (10.7)	101 (21.9)	152 (14.8)	190 (20.9)	246(14.7)	0.001
Alcohol	147 (2.3)	9 (1.2)	27 (4.1)	9 (1.2)	7 (1.5)	38 (3.7)	29 (3.2)	28 (1.7)	0.001
Educational status									
Illiterate	1860 (29.6)	309 (38.8)	221 (35.9)	214 (29.0)	337 (72.9)	237 (23.1)	125 (13.8)	417 (25.6)	
Primary school	2267 (36.1)	280 (35.2)	196 (31.9)	391 (53.0)	102 (22.1)	429 (41.9)	216 (26.8)	653 (40.1)	
Secondary school	802 (12.8)	74 (9.3)	127 (20.7)	47 (6.4)	9 (1.9)	138 (13.5)	164 (18.1)	243 (14.9)	0.001
High school	890 (14.2)	95 (11.9)	66 (10.7)	49 (6.6)	11 (2.4)	156 (15.2)	283 (31.2)	230 (14.1)	
University or higher	350 (5.6)	38 (4.8)	5 (0.8)	37 (5.0)	3 (0.6)	64 (6.3)	119 (13.1)	84 (5.2)	
Atrial fibrillation type									
First attack	290 (4.6)	14 (1.8)	44 (6.7)	16 (2.2)	16 (3.5)	26 (2.5)	11 (1.2)	163 (10.0)	
Paroxysmal	859 (13.7)	92 (11.6)	117 (17.7)	96 (12.9)	45 (9.7)	139 (13.6)	64 (7.1)	306 (18.8)	0.001
Persistent/permanent	5066 (80.7)	690 (86.7)	500 (75.6)	631 (84.9)	401 (86.8)	858 (83.9)	828 (91.7)	1158 (71.2)	
Creatinine, median, IQR	0.9 (0.8–1.1)	0.9 (0.8–1.1)	1.0 (0.9–1.2)	0.9 (0.7–1.0)	0.9 (0.8–1.2)	0.9 (0.8–1.1)	0.9 (0.8–1.1)	1.0 (0.8–1.1)	0.001
Creatinine clearance, mL/min	74.5±31.38	70.6±15.7	66.6±16.5	72.3±22.7	70.0±16.8	71.9±17.2	77.7±17.8	72.8±19.9	0.001
Place of residence									
Rural	2153 (34.3)	435 (54.6)	292 (47.9)	427 (57.9)	198 (43)	196 (19.1)	352 (38.8)	253 (15.1)	0.001
Urban	4051 (64.7)	361 (45.4)	318 (52.1)	310 (42.1)	262 (57)	828 (80.9)	555 (61.2)	1417 (84.9)	
COPD	1448 (23.1)	179 (22.5)	221 (33.7)	212 (29.2)	137 (29.7)	212 (20.7)	153 (16.9)	334 (19.9)	0.001
Coronary heart disease	1828 (29.1)	281 (35.3)	215 (32.8)	157 (21.1)	158 (34.2)	331 (32.4)	275 (30.3)	411 (24.5)	0.001
Congestive heart failure	1386 (22.1)	188 (23.6)	142 (21.5)	160 (21.5)	168 (36.4)	204 (19.9)	204 (22.5)	320 (19.2)	0.001
Hypertension	4305 (68.6)	646 (81.3)	490 (74.1)	556 (74.8)	268 (58.1)	730 (71.4)	519 (57.3)	1096 (65.4)	0.001
Diabetes mellitus	1389 (22.1)	176 (22.1)	146 (22.1)	154 (20.8)	71 (15.4)	281 (27.4)	192 (21.2)	369 (22)	0.001
Stroke/Transient ischemic attack	835 (13.3)	103 (13)	122 (18.6)	120 (16.1)	43 (9.4)	78 (7.6)	112 (12.3)	257 (15.4)	0.001
Vascular disease	1506 (24.0)	198 (25.5)	196 (29.6)	166 (22.4)	139 (30.1)	219 (21.4)	249 (27.5)	339 (20.3)	0.001
Bleeding history									0.001
Major	305 (4.8)	38 (4.8)	25 (3.8)	25 (3.4)	17 (3.7)	73 (7.2)	61 (6.7)	66 (4.1)	
Minor	1050 (16.7)	184 (23.2)	104 (15.7)	95 (12.9)	46 (10)	261 (25.8)	148 (16.3)	212 (13.3)	
CHA_2DS_2VASc	3.28±1.59	3.46±1.47	3.47±1.53	3.53±1.52	3.29±1.46	3.22±1.57	3.11±1.62	3.11±1.68	0.001
Low stroke risk*	364 (5.8)	27 (3.4)	14 (2.1)	25 (3.4)	32 (6.9)	38 (3.9)	71 (7.8)	157 (9.4)	
Medium stroke risk*	945 (15.1)	111 (14.0)	79 (12.0)	89 (12.0)	58 (12.6)	169 (17.1)	171 (18.9)	268 (16.1)	0.001
High stroke risk*	4912 (78.3)	654 (82.6)	567 (85.9)	630 (84.7)	372 (80.5)	780 (79.0)	665 (73.3)	1244 (74.5)	
HAS-BLED	1.65±1.08	1.71±0.98	1.95±1.12	1.75±0.91	1.7±1.02	1.3±1.11	1.7±1.12	1.64±1.08	0.001

CHA_2DS_2VASc - Congestive heart failure or left ventricular dysfunction, Hypertension, Age ≥75 years, Diabetes, prior thromboembolism or Stroke, Vascular disease, Age 65–74 years, Sex category; COPD - Chronic obstructive pulmonary disease; HAS-BLED - Hypertension, Abnormal renal or liver function, Stroke history, Bleeding history, Labile international normalized ratio, Elderly (age >65 years), Drugs or alcohol use. Values are given as mean±standard deviation or number (percentage) unless otherwise indicated. *Stroke risk was categorized according to CHA_2DS_2VASc scores: low stroke risk: CHA_2DS_2VASc, 0 for male and CHA_2DS_2VASc ≤1 for female; medium stroke risk: CHA_2DS_2VASc, 1 for male and CHA_2DS_2VASc, 2 for female; high stroke risk: CHA_2DS_2VASc, ≥2 for male and CHA_2DS_2VASc, ≥3 for female

Table 2. Comparison of the stroke prevention strategies and antiarrhythmic therapies among the seven geographical regions of Turkey

	Overall 6273	Mediterrannean 796 (12.7%)	East Anatolia 662 (10.6%)	Aegean 745 (11.9%)	Southeast Anatolia 462 (7.4%)	Central Anatolia 1024 (16.3%)	Black Sea 907 (14.5%)	Marmara 1677 (26.7%)	*P*
Anticoagulant therapy									
No anticoagulant	1716 (27.3)	315 (39.7)	310 (46.8)	177 (23.8)	236 (51.1)	123 (12.0)	184 (20.3)	371 (22.1)	0.001
VKA, warfarin	2173 (34.6)	287 (36.1)	117 (17.7)	233 (31.3)	91 (19.7)	609 (59.5)	121 (13.3)	715 (42.6)	0.001
NOAC	2340 (37.3)	192(24.2)	214(33.4)	333(44.8)	135(29.2)	280(27.7)	601(66.3)	585(35)	0.001
Dabigatran	1148 (18.3)	90 (11.3)	83 (12.5)	184 (24.7)	77 (16.7)	144 (14.1)	356 (39.3)	214 (12.8)	0.001
Rivaroxaban	942 (15.0)	72 (9.0)	100 (15.1)	141 (18.9)	53 (11.5)	105 (10.3)	174 (19.2)	297 (17.7)	0.001
Apixaban	250 (3.9)	30 (3.8)	31 (4.7)	8 (1.1)	5 (1.1)	31 (3.0)	71 (7.8)	74 (4.4)	0.001
Antiplatelet therapy									
Acetylsalicilic acid	1624 (25.9)	230 (28.9)	228 (34.4)	172 (23.1)	225 (48.7)	217 (21.2)	260 (28.7)	292 (17.4)	0.001
Clopidogrel, prasugrel, or ticagrelor	231 (3.7)	45 (5.7)	24 (3.6)	14 (1.9)	19 (4.1)	21 (2.1)	50 (5.5)	58 (3.5)	0.001
Dual antiplatelet therapy	155 (2.5)	33 (4.1)	29 (4.4)	23 (3.1)	8 (1.7)	23 (2.2)	25 (2.8)	14 (0.8)	0.001
OAC + antiplatelet therapy	818 (13.2)	88 (11.1)	69 (11.0)	82 (11.1)	71 (15.4)	173 (17.1)	185 (20.4)	150 (9.1)	<0.001
Drugs for rate/rhythm control									
Beta blocker	3931 (62.6)	554 (69.7)	388 (58.9)	472 (64.6)	282 (61.0)	733 (71.6)	502 (55.3)	1000 (61.6)	0.001
Non-DHP CCB	1466 (23.3)	149 (18.8)	143 (22.2)	150 (20.5)	100 (21.6)	273 (26.7)	327 (36.1)	324 (20.0)	0.001
Digoxin	1274 (20.3)	182 (22.9)	124 (18.9)	208 (28.4)	128 (27.7)	274 (26.8)	127 (14.0)	231 (14.2)	0.001
Amiodarone	298 (4.7)	35 (4.4)	13 (2.1)	35 (4.8)	14 (3.0)	67 (6.5)	53 (5.9)	81 (5.0)	0.001
Propafenone	178 (2.8)	21 (2.6)	22 (3.4)	11 (1.5)	14 (3.0)	29 (2.8)	21 (2.3)	60 (3.7)	0.100
Sotalol	56 (0.8)	6 (0.8)	3 (0.5)	9 (1.2)	0 (0)	12 (1.2)	16 (1.8)	10 (0.6)	0.012

NOAC - non-vitamin K antagonist oral anticoagulant; Non-DHP CCB - non-dihydropyridine calcium channel blocker; VKA, Vitamin K antagonist

Table 3. Appropriateness of anticoagulant therapy in the seven geographical regions of Turkey

	Mediterranean 796 (12.7%)	East Anatolia 662 (10.6%)	Aegean 745 (11.9%)	Southeast Anatolia 462 (7.4%)	Central Anatolia 1024 (16.3%)	Black Sea 907 (14.5%)	Marmara 1677 (26.7%)	*P*
Appropriate treatment	485 (61.3)	338 (52.8)	578 (77.9)	238 (51.5)	831 (85.2)	677 (74.7)	1211 (72.7)	<0.001
Inappropriate treatment	306 (38.7)	302 (47.2)	164 (22.1)	224 (48.5)	144 (14.8)	229 (25.3)	454 (27.3)	<0.001
Undertreatment	296 (37.4)	299 (46.7)	158 (21.3)	214 (46.3)	115 (11.8)	171 (18.9)	333 (20.0)	<0.001
Overtreatment	10 (1.3)	3 (0.5)	6 (0.8)	10 (2.2)	29 (3.0)	58 (6.4)	121 (7.3)	<0.001

Anatol J Cardiol 2017; 18: 273-80
DOI:10.14744/AnatolJCardiol.2017.7709

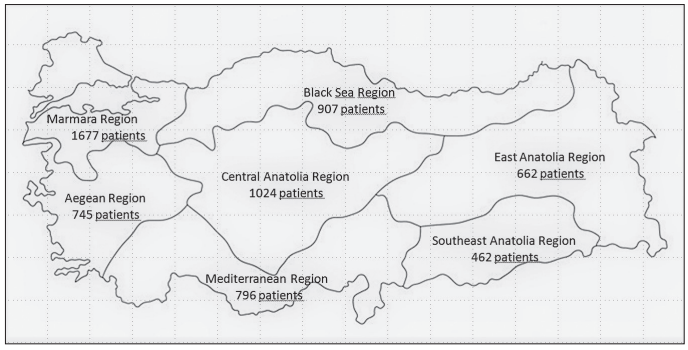

Figure 1. Regional distribution of patients

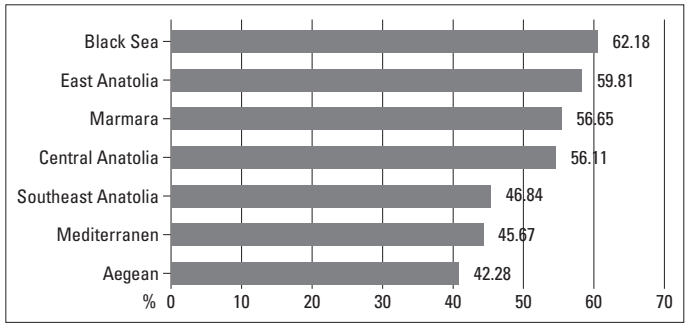

Figure 2. The distribution of mean TTR values among the seven geographical regions

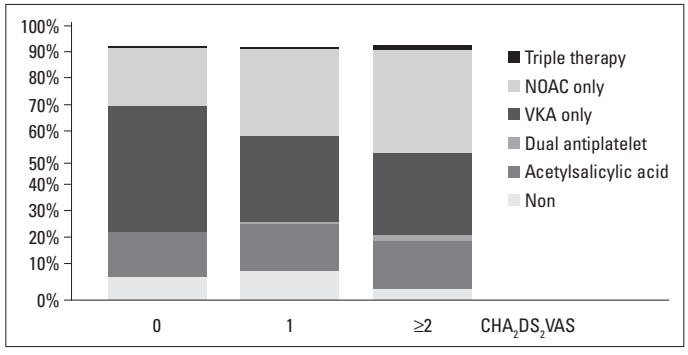

Figure 3. The use of antithrombotic medications according to the stroke risk groups

were unnecessarily using warfarin, NOAC, or antiplatelet agents. The proportion of patients not prescribed Oac therapy was highest in Southeast Anatolia (51.1%) and East Anatolia (46.8%). Similarly, the prescription rates of antiaggregants in East and Southeast Anatolia were found to be higher than in all other regions. After excluding 92 patients whose data were absent for the evaluation of appropriateness of OAC therapy, data of 6181 patients were analyzed to find out the differences in guideline-adherent use of anticoagulant therapy among the seven regions of Turkey.

Treatment appropriateness and under- and overtreatment rates in the different regions are presented in Table 3. Among 6181 patients, 1823 (29.5%) were inappropriately treated. Inappropriate use was most prevalent in East and Southeast Anatolia, and the most guideline-adherent use of OACs was detected in Central Anatolia.

Discussion

The main findings of the present sub-study of the RAMSES study revealed the first cross-sectional data on the sociodemographic, lifestyle, clinical, and treatment characteristics of patients with NVAF in Turkey.

The most significant findings of the present study are as follows. First, differences were detected between the seven geographical regions of Turkey in terms of several baseline clinical characteristics and baseline frequencies of OAC utilization. Second, although the mean CHA_2DS_2VASc score was >3, nearly half of the patients received no anticoagulant therapy in East and Southeast Anatolia. Third, the highest prevalence of inappropriate use was noted in East and Southeast Anatolia, which are also the least socioeconomically developed regions of the country.

What is already known on this topic?

AF is a major public health burden worldwide, and its prevalence is expected to increase because of widespread population aging, particularly in developing countries such as Turkey. Although epidemiological data on the prevalence or management strategies of AF are available in USA and Europe, such data are limited in our country. The geographical heterogeneity of AF has been suggested in previous studies (15). Realise AF survey that enrolled 10546 AF patients from 831 sites in 26 countries showed that AF patients from the Middle East and Africa were significantly younger and were more frequently females compared with the patients in the rest of the world (15).

A $CHADS_2$ score ≥2 was observed in 64.2% of the patients enrolled from Europe, whereas it was 58.3%, 57.8%, and 43.6% in Latin America, Asia, and the Middle East and Africa, respectively. Among those patients with $CHADS_2$ score ≥2, there were important geographical differences in terms of the use of antithrombotics: the proportion of patients not receiving any antithrombotic agent varied between 11.4% in the Middle East and Africa to 27.6% in Latin America. The ADHERE-International registry reporting data of 2358 patients with AF from 10 Asia-Pacific and Latin American countries demonstrated that the highest and lowest rates of OAC use were in Australia (65.2%) and Taiwan (25.1%), respectively (16). The results of the ADHERE-International and Realise AF studies have shown that the proportion of patients with AF treated with OAC therapy varies between different countries, and the intensity and quality of warfarin-based anticoagulant therapy also differs between geographical regions around the world. Moreover, regional differences were detected in the proportions of patients with AF treated with warfarin for the prevention of thromboembolism in the USA and Japan (17, 18).

In a previous study investigating warfarin use in patients with AF in the USA, the lowest frequency of warfarin use was noted in the southern part of the USA (17). Similarly, regional differences in the frequency of warfarin use were statistically significant in Japan, with the lowest use seen in Hokkaido, followed by Shikoku

(18). Baseline INR and TTR also significantly differed between the regions in Japan (18). However, there is limited knowledge on the regional differences in frequency of warfarin or NOAC use or guideline adherence of management among patients with NVAF in Turkey. The only multicentral AF study in our country is the AFTER registry (19). In that study, 2242 consecutive patients were recruited from 17 referral hospitals, reflecting the overall population of the seven geographical regions of Turkey. Although 87% of the patients were found to have a high risk of stroke, OAC therapy was used only in 40% of the patients. However, that study was performed before the NOAC era, and the authors did not evaluate the results of the seven regions of Turkey separately. Although the availability of NOACs provide a significant opportunity to address some of the limitations associated with VKAs in the current anticoagulant therapy management, previous studies have shown that the rate of OAC prescriptions still remains to be low because of physicians' perceptions about bleeding in our country (5, 20). Moreover, inappropriate drug utilization is frequent among patients with NVAF not only for warfarin but also for NOACs, and anticoagulation quality is still poor in Turkey (5, 20). A commonly used summary of the quality of VKA anticoagulation is the linearly interpolated percent TTR; it must be >65% for better anticoagulation (1), but even in the best regions of our country, the TTR value was still <65%. Our study showed that the quality of anticoagulation with VKA greatly differed among the seven regions, and interestingly the lowest TTR was observed in Aegean. However, people living in Aegean were older than those in the other regions and Aegean has the highest proportion of patients living in rural areas. Our study showed that the highest TTR value was in patients living in Black Sea with 62.2%. However, only 13.3% of the patients were on VKA therapy in this region.

Clinical implications

The RAMSES study has shown that considerable differences in patient characteristics and case management exist between the geographical regions of Turkey, reflecting variations in social, cultural, and organizational aspects. Outcomes of NVAF may be worse in eastern regions, and the use of treatment algorithms may be much more useful to guide optimal treatment strategy. The presence of differences in these regions indicates areas where education may be useful to ensure the most appropriate management of patients with NVAF.

Study limitations

This was an observational analysis of the registry data. Clinical outcomes such as stroke, mortality, and re-hospitalization were not evaluated in the registry. Therefore, we were not able to investigate the consequences of under-utilization of anticoagulation in this patient population. Moreover, the study did not examine the extent to which any of the abovementioned AF-related outcomes were influenced by demographic/disease characteristics.

Another limitation of this study was the cross-sectional design, which may have resulted in potential biases and missing data.

Conclusion

The RAMSES study was the first study to show significant regional differences in the clinical characteristics and the management of patients with NVAF among the seven geographical regions of Turkey. Frequency of warfarin and NOAC utilization, intensity and quality of warfarin treatment, and the appropriateness of OAC therapy in patients with NVAF varied between the different geographical regions. Patients living in the eastern regions (Southeast Anatolia and East Anatolia) had substantially poor management of AF. Urgent future research is required to investigate how this considerable treatment deficit regarding AF in the eastern population impacts the management of patients living in those regions. There is a need for effective interventions to address the management gap between eastern and western populations of patients with AF in Turkey. Specialized anticoagulation units may provide an opportunity to standardize the management of anticoagulation and improve the quality of stroke prevention in the eastern regions of Turkey.

Appendix (*numbers indicate cities)

Collaborators*: Sedat Kalkan[1], Ahmet İlker Tekkesin[2], Yasin Çakıllı[3], Ceyhan Türkkan[2], Vahit Demir[4], Feyza Çalık[5], Oğuz Karaca[6], Füsun Helvacı[7], Mehmet Aytürk[8], Kadriye Akay[9], Yiğit Çanga[10], Savaş Çelebi[11], Emine Altuntaş[12], Hacı Murat Güneş[6], Tahir Bezgin[13], Aytekin Aksakal[14], Beytullah Çakal[6], Ayşe Çolak[15], Özgür Kaplan[16], Adem Tatlısu[17], Gökhan Gözübüyük[16], Selami Demirelli[18], Adnan Kaya[19], İbrahim Rencüzoğulları[20], Zübeyde Bayram[10], Zeki Şimşek[10], Murat Civan[21], Ulaankhu Batgharel[22], Ali Ekber Ata[23], Gökhan Göl[24], Gurbet Özge Mert[25], Kadir Uğur Mert[25], Aleks Değirmencioğlu[26], Özkan Candan[27], Özlem Özcan Çelebi[28], Cem Doğan[16], Fethi Yavuz[29], Şeref Ulucan[30], Arif Arısoy[31], Bingül Dilekçi Şahin[18], Emrah Ermiş[18], Serkan Gökaslan[32], İdris Pektaş[33], Aslı Tanındı[34], Kamuran Tekin[35], Kadriye Memic Sancar[25], İbrahim Altun[25], Edip Güvenç Çekiç[36], Nesrin Filiz Başaran[36].

The cities involved in the collaboration: [8,11,28,34]Ankara, [2,3,6,7,26,21,10,22,24,32]İstanbul, [5,33]Mersin, [1]Balıkesir-Gönen, [4]Yozgat, [15]Mersin-Mut, [9]Kocaeli, [13]Kocaeli-Gebze, [12]Bingöl, [14]Samsun, [16]Malatya, [17]Sivas, [18]Erzurum, [19]Şanlıurfa-Suruç, [20]Kars, [23]Samsun, [25]Muğla, [27]Uşak, [29]Gaziantep, [30]Konya, [31]Tokat, [35]Batman, [36]Muğla

Conflict of interest: None declared.

Peer-review: Externally peer-reviewed.

Acknowledgements: The authors would like to thank Ekrem Bilal Karaayvaz, MD, Bağcılar Education and Research Hospital, Department of Cardiology, Mevlüt Koç, MD, Assoc. Prof, Adana Numune Education and Research Hospital, Department of Cardiology, Durmuş Yıldıray Şahin, MD, Assoc. Prof, Adana Numune Education and Research Hospi-

Anatol J Cardiol 2017; 18: 273-80
DOI:10.14744/AnatolJCardiol.2017.7709

tal, Department of Cardiology, Tolga Çimen, MD, Dışkapı Yıldırım Beyazıt Education and Research Hospital, Department of Cardiology, Tolga Sinan Güvenç, MD, Siyami Ersek Heart Education and Research Hospital, Department of Cardiology, Nihat Pekel, MD, Assist Prof, İzmir Medikal Park Hospital, Department of Cardiology, Kerem Temel, MD, Acıbadem Eskişehir Hospital, Department of Cardiology, Vehip Keskin, MD, Muğla Private Cardiology Clinic for their contribution to the study.

References

1. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al: 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS: The Task Force for the management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC Endorsed by the European Stroke Organisation (ESO). Eur Heart J 2016 ;37:2893-962.
2. Durrant J, Lip GY, Lane DA. Stroke risk stratification scores in atrial fibrillation: current recommendations for clinical practice and future perspectives. Expert Rev Cardiovasc Ther 2013;11:77-90.
3. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. Chest 2010;137:263-72.
4. Başaran Ö, Beton O, Doğan V, Tekinalp M, Aykan AÇ, Kalaycıoğlu E, et al. ReAl-life Multicenter Survey Evaluating Stroke prevention strategies in non-valvular atrial fibrillation (RAMSES study), Anatol J Cardiol 2016;16:734-41.
5. Başaran Ö, Doğan V, Beton O, Tekinalp M, Aykan AC, Kalaycıoğlu E, et al. Suboptimal use of non-vitamin K antagonist oral anticoagulants: Results from the RAMSES study. Medicine (Baltimore) 2016;95:e4672.
6. Agarwal S, Bennett D, Smith DJ. Predictors of warfarin use in atrial fibrillation patients in the inpatient setting. Am J Cardiovasc Drugs 2010;10:37-48.
7. Lewis WR, Fonarow GC, LaBresh KA, Cannon CP, Pan W, Super DM, et al. Differential use of warfarin for secondary stroke prevention in patients with various types of atrial fibrillation. Am J Cardiol 2009;103:227-31.
8. Wong ND. Epidemiological studies of CHD and the evolution of preventive cardiology. Nat Rev Cardiol 2014;11:276–89.
9. Özaslan M, Dinçer B, Özgür H. Regional Disparities and Territorial Indicators in Turkey: Socio-Economic Development Index (SEDI) Enlargement, Southern Europe, and the Mediterranean, Volos, Greece: The department of planning and regional development, University of Thessaly and the Greek section of ERSA, Paper presented at: 46th Congress of the European Regional Science Association (ERSA); Volos, Greece 2006.
10. Çelebioğlu F, Dall'erba S. Spatial disparities across the regions of Turkey: an exploratory spatial data analysis. Ann Reg Sci 2010; 45:379-400.
11. Başkent University/Ministry of Health/Refik Saydam Hygiene Center Presidency, School of Public Health (2004) National Burden of Disease and Cost Effectiveness Project – Final Report, 1st ed. http://ekutuphane.sagem.gov.tr/kitaplar/turkey_burden_of_disease_study.pdf Accessed 25.08. 2014
12. Uyarel H, Onat A, Yüksel H, Can G, Ordu S, Dursunoğlu D. Incidence, prevalence, and mortality estimates for chronic atrial fibrillation in Turkish adults. Turk Kardiyol Dern Ars 2008;36:214-22.
13. Başaran Ö, Doğan V, Memic Sancar K, Altun İ, Mert KU, Mert GÖ, et al; RAMSES investigators. Rationale, design and methodology of the RAMSES Study: ReAl-life Multicenter Survey Evaluating Stroke Prevention Strategies. Turk Kardiyol Dern Ars 2016;44:215-20.
14. Schulman S, Kearon C; Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost 2005;3:692–4.
15. Chiang CE, Naditch-Brûlé L, Murin J, Goethals M, Inoue H, O'Neill J, et al. Distribution and risk profile of paroxysmal, persistent, and permanent atrial fibrillation in routine clinical practice: insight from the real-life global survey evaluating patients with atrial fibrillation international registry. Circ Arrhythm Electrophysiol 2012;5:632-9.
16. Suarez J, Piccini JP, Liang L, Atherton JJ, Hayward CS, Krum H, et al. International variation in use of oral anticoagulation among heart failure patients with atrial fibrillation. Am Heart J 2012;163:804-11.
17. Stafford RS, Singer DE. National patterns of warfarin use in atrial fibrillation. Arch Intern Med 1996;156: 2537-41.
18. Inoue H, Atarashi H, Kodani E, Okumura K, Yamashita T, Origasa H, et al; J-RHYTHM Registry Investigators. Regional differences in frequency of warfarin therapy and thromboembolism in Japanese patients with non-valvular atrial Fibrillation - Analysis of the J-RHYTHM Registry. Circ J 2016;80:1548-55.
19. Ertaş F, Eren NK, Kaya H, Arıbaş A, Acar G, Kanadaşı M, et al; for the AFTER Investigators. The atrial fibrillation in Turkey: Epidemiologic Registry (AFTER). Cardiol J 2013;20:447-52.
20. Başaran O, Filiz Başaran N, Cekiç EG, Altun I, Doğan V, Mert GO, et al. PRescriptiOn PattERns of Oral Anticoagulants in Nonvalvular Atrial Fibrillation (PROPER study). Clin Appl Thromb Hemost 2017;23:384-91.