

Oral Anticoagulant Use and Long-Term Follow-Up Results in Patients with Non-valvular Atrial Fibrillation in Turkey AFTER-2 Study

ABSTRACT

Background: The aim of this study was to investigate the frequency of oral anticoagulant drugs and time in therapeutic range in patients receiving warfarin in addition to the epidemiological trial of non-valvular atrial fibrillation previously conducted in Turkey (The Atrial Fibrillation: Epidemiological Registry trial). Furthermore, the prevalence of major adverse events and mortality rates of the patients were evaluated during the long-term follow-up period.

Methods: We created a national data registry for non-valvular atrial fibrillation patients, reflecting all geographic regions by population density. In that context, the study included all consecutive atrial fibrillation patients older than 18 years of age who were admitted to the cardiology outpatient clinic except for patients those with prosthetic heart valves and rheumatic mitral valve stenosis.

Results: This study included 2592 patients from 35 different centers. The mean age was 68.7 ± 11.1 years, and 55.5% of the patients were female. The most common comorbid diseases were chronic kidney disease (69%) and hypertension (65.5%). The time in therapeutic range rate in the general population was 40%, and the mortality rate at 5-year follow-up was 29.4%.

Conclusion: The Atrial Fibrillation: Epidemiological Registry 2 study showed higher use of anticoagulant in non-valvular atrial fibrillation patients than in previous national studies. Furthermore, this study demonstrated that most of the non-valvular atrial fibrillation patients are in the high-risk group and the time in therapeutic range rates are still low in Turkey. As a result, this is a significant reason for switching from warfarin to non-K vitamin-dependent new oral anticoagulant treatments.

Keywords: Atrial fibrillation, oral anticoagulant therapy, epidemiology, mortality

INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia in adults worldwide. The estimated prevalence of AF in adults is between 2% and 4%.¹ According to the results of the TEKHARF (Cardiac Diseases and Risk Factors in Adults in Turkey) study, the prevalence of AF in our country is 1.25% and its general morbidity is 6.8/100 person-years.² And it is an important health problem in our country.² Risk factors such as advanced age, hypertension (HT), diabetes mellitus (DM), heart failure, coronary artery disease, chronic kidney disease, obesity, and sleep apnea increase the risk of AF.¹ Due to the longer life expectancy in the general population and the intensification of research for undiagnosed AF, a 2- to 3-fold increase in the prevalence of AF is expected.¹ However, the incidence of AF-related events, and especially thromboembolic events, is increasing. Risk stratification is important when considering anticoagulation, as the risk of stroke in AF patients depends on clinical determinants. CHA2DS2-VASc (heart failure, HT, age >75, diabetes, stroke, vascular disease, 65-74 age, and gender category female) risk score classification is widely used in our clinical practice to determine stroke risk.³ Conventional treatment with vitamin K antagonists (VKA) in patients with non-valvular AF is replaced by non-vitamin K antagonist new oral anticoagulants (NOAC), either direct factor Xa inhibitors or direct thrombin inhibitors.³ The

ORIGINAL INVESTIGATION

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Atrial Fibrillation: Epidemiological Registry (AFTER) study in Turkey, which is the first multicenter study conducted on AF patients in our country, showed that 40% of non-valvular AF (NVAF) patients were on warfarin treatment, but only 37% of these patients were in the effective international normalized ratio (INR) range; however, the most common reason for inadequate use of warfarin was physician negligence.⁴ In addition to the risk of stroke, it is important to control the rate or rhythm in the selected patient group to define the cardiovascular risk profile and to give optimal medical treatment. In the REALISE AF study conducted in this respect, it was observed that AF control could not be achieved at an optimal level and this situation led to the frequency of symptoms in patients, leading to deterioration in functional status and quality of life.⁵ In addition, it has been determined that it causes an increase in the need for hospital admission and intervention due to cardiovascular events.⁵ With the AFTER-2 study we have done, in addition to the epidemiological data of NVAF patients in Turkey, we wanted to examine the frequency and type of oral anticoagulant treatment, the rate of staying at effective INR levels in patients receiving warfarin, and the treatment management adopted. In addition, we aimed to determine the frequency of major adverse events and mortality rates in the long-term follow-up of the patients.

METHODS

Study Design

The design of this study was previously published in 2015.⁶ While selecting patients for the study, under the leadership of our institution, 2592 patients from 35 different centers were included according to the population density of the regions. The study included all consecutive NVAF patients older than 18 years of age who were admitted to the cardiology outpatient clinic except for patients those with prosthetic heart valves and rheumatic mitral valve stenosis. In addition, patients in centers whose follow-up data could not be accessed and consent forms were missing were excluded from the study. Each patient or his/her trustee was informed about the study both orally and in written form. Patients

were included in the study according to the Statistical Regional Units Classification, reflecting the population of 12 regions of Turkey.

Patient Characteristics and Follow-Up Data

The AFTER-2 study was designed as a prospective, observational, multicenter epidemiological study with 1- and 5-year patient follow-ups. The patients to be included in the study were informed, and after each patient signed an informed consent form, the case report form prepared for each patient was filled in by the researchers. Atrial fibrillation type was evaluated in terms of demographic data, comorbid diseases, echocardiographic data, time in therapeutic range (TTR) data, anticoagulant treatments and other medical treatments, hemogram parameters, biochemical parameters, and long-term follow-up data. Routine hemogram, biochemical parameters, and INR values were studied in each center's own laboratory. Glomerular filtration rate values were calculated based on the Cockcroft–Gault formula. The percentage of time in the therapeutic INR range was calculated according to the Roosendaal method, assuming that the changes (at least 6) between consecutive INR measurements were linear with time.⁷ The target TTR level was considered >60% as recommended by the guidelines. Major bleeding according to the criteria of the International Society for Thrombosis and Hemostasis is defined as symptomatic and/or mortal bleeding in critical areas or organs that results in a decrease in hemoglobin of at least 2 g/dL, resulting in 2 or more transfusions of whole blood or red blood cells (e.g., with intracranial, intraspinal, intraocular, retroperitoneal, pericardial, intraarticular, or intramuscular compartment syndrome).⁸ It was evaluated with the CHA2DS2-VASc score for stroke risk and the HASBLED score for bleeding risk. Based on primary endpoints at 1- and 5-year follow-ups, transient ischemic attack (TIA), hemorrhagic cerebrovascular occlusion, and mortality were analyzed. Follow-up data were obtained from hospital registry systems and national data recording systems. Study approval was obtained by the Local Ethics Committee (Date and number: December 26, 2014-47).

Statistical Analysis

Data were analyzed with the Statistical Package for the Social Sciences (SPSS) software version 25.0 for Windows (SPSS Inc, Chicago, Ill, USA). The Kolmogorov–Smirnov test was used to confirm the normality of the distribution of continuous variables. Continuous variables were indicated as mean \pm standard deviation (SD) or median (interquartile range). Categorical variables were indicated as percentages and were compared using Chi-square test or Fisher's exact test as appropriate. Continuous variables between 2 independent groups were analyzed by Student's *t*-test or Mann–Whitney *U* test as appropriate. Univariate and multivariate Cox regression analyses were performed to identify predictors of primary endpoints and also were plotted in graphs (Figure 1, 2). Kaplan–Meier test (log rank) was performed to determine event-free survival between groups. Variables with a *P*-value of <.05 were considered significant.

HIGHLIGHTS

- We shared the 5-year follow-up results of 2592 non-valvular atrial fibrillation (NVAF) patients from 35 different centers. We found all-cause mortality to be 29.4%.
- Most NVAF patients were in the high-risk group for the CHA2DS2-VASc score risk classification. More than three-quarters of these patients were receiving oral anticoagulation therapy.
- As the risk class of the CHA2DS2-VASc score increased, the frequency of adverse events and mortality increased significantly.
- The time in therapeutic range rates in Turkey are still low. This is an important factor in increasing the transition from warfarin therapy to new oral anticoagulant therapies.

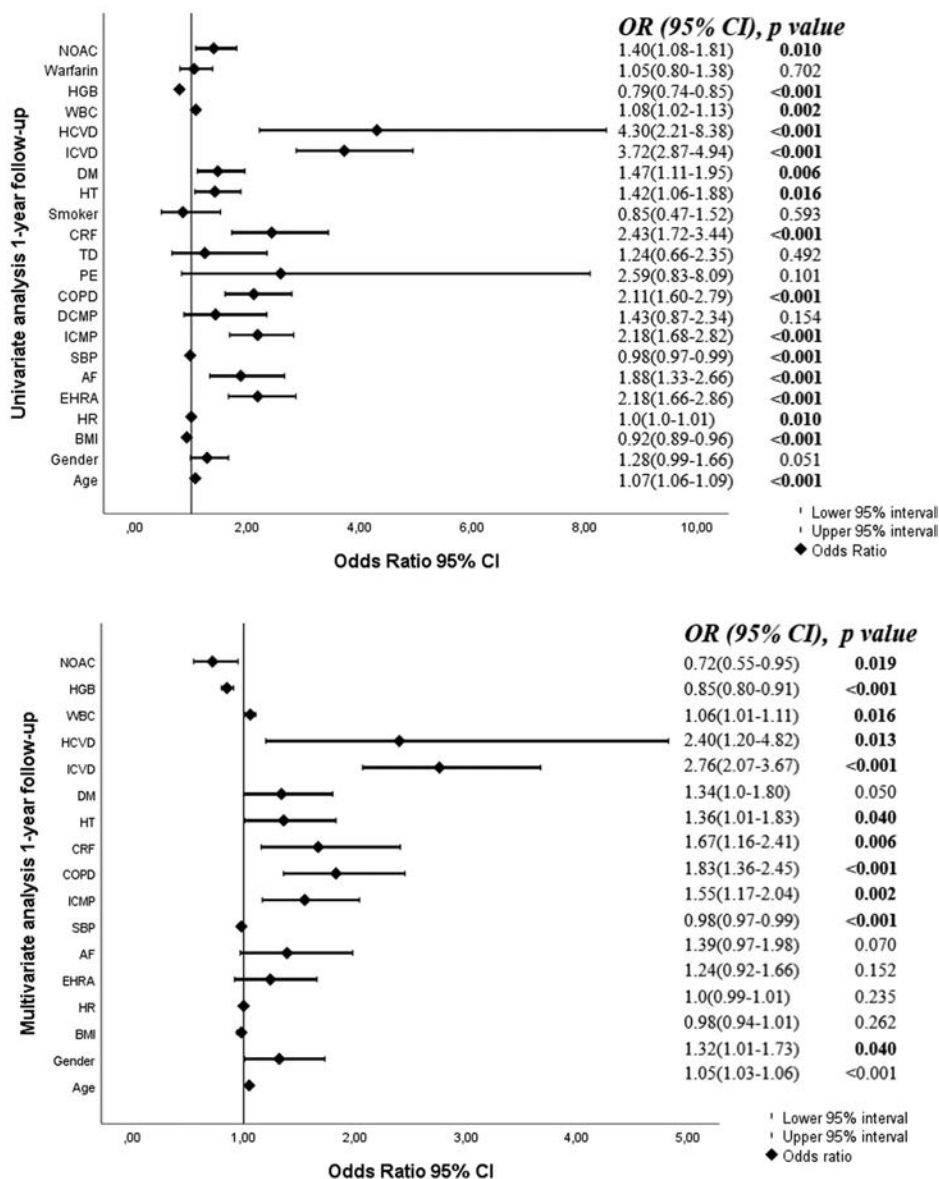


Figure 1. Cox regression analysis results at first-year follow-up. BMI, body mass index; HR, heart rate; EHRA, European Heart Rhythm Association; AF, atrial fibrillation; SBP, systolic blood pressure; ICMP, ischemic cardiomyopathy; DCMP, dilated cardiomyopathy; COPD, chronic obstructive pulmonary disease; PE, pulmonary embolism; TD, thyroid dysfunction; CRF, chronic renal failure; HT, hypertension; DM, diabetes mellitus; ICVD, ischemic cerebro vascular disease; HCVD, hemorrhagic cerebrovascular disease; WBC, white blood cell; HGB, hemoglobin; NOAC, new oral anticoagulant.

RESULTS

A total of 2592 patients were included in the study. According to CHA2DS2-VASc score risk classification, 349 patients were in the low-intermediate risk group and 2243 patients were in the high-risk group. Among all patient groups, the proportion of female patients was higher (55.5%). The rate of men (69.9%) in the low-intermediate risk group and the rate of women (59.4%) in the high-risk group were significantly higher. While the mean age was 68.7 ± 11.1 years among all patient groups, the age was significantly higher in the high-risk group (70.5 ± 9.4 years, $P < .001$). The most common diseases were chronic renal failure (CRF) (69%), hypertension (65.5%), ischemic cardiomyopathy (26%), and DM (22.2%),

respectively, in all groups. The ejection fraction (EF) rate was found to be 50.5 ± 10.7 in all patient groups. The EF rate was significantly higher in the low-intermediate risk group ($55.5 \pm 7.8\%$) compared to the high-risk group (49.8 ± 10.9) ($P < .001$) (Table 1). Other demographic characteristics, comorbid diseases, and echocardiographic results in the study are summarized in Table 1.

In terms of AF type, permanent AF was detected most frequently (64.2%). It was significantly higher in the high-risk group (68.2%) than in the low-intermediate risk group (38.4%) ($P < .001$). The patients who applied were predominantly in the class-2 category (57.8%) according to the European Heart Rhythm Association (EHRA) classification.

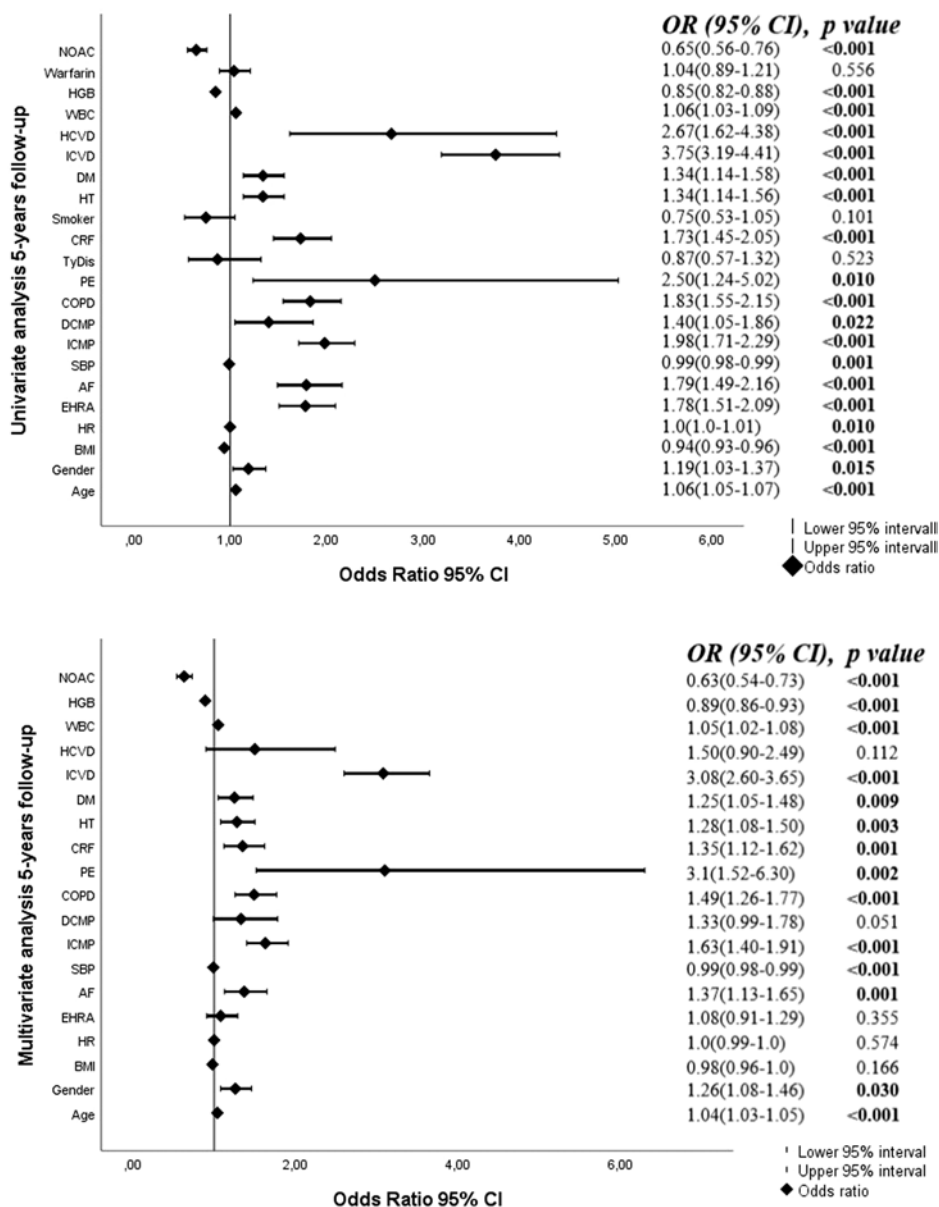


Figure 2. Cox regression analysis results at 5-year follow-up. BMI, body mass index; HR, heart rate; EHRA, European Heart Rhythm Association; AF, atrial fibrillation; SBP, systolic blood pressure; ICMP, ischemic cardiomyopathy; DCMP, dilated cardiomyopathy; COPD, chronic obstructive pulmonary disease; PE, pulmonary embolism; TyDis, thyroid dysfunction; CRF, chronic renal failure; HT, hypertension; DM, diabetes mellitus; ICVD, ischemic cerebrovascular disease; HCVD, hemorrhagic cerebrovascular disease; WBC, white blood cell; HGB, hemoglobin; NOAC, new oral anticoagulant.

In addition, those presenting with EHRA class 2 were significantly higher in the high-risk group (59.1%) than in the low-intermediate risk group (49.3%) ($P < .001$). Rhythm control (75.7%) was the most preferred treatment strategy among the patients (Table 2).

The mean follow-up period of the patients was 1920 days. Ischemic cerebrovascular disease (CVD) rate (6.1% vs. 1.7%, $P = .001$), mortality rate at 1-year follow-up (10.3% vs. 1.7%, $P < .001$), mortality rate at 5-year follow-up (32.3% vs. 10.3%, $P < .001$) and HASBLED score ($P < .001$) were significantly higher in the high-risk group than in the low risk group. The rate of hemorrhagic CVD was also found to be higher in the

high-risk group. In addition, in the general population, the mortality rate at 1-year follow-up was 9.1%, and the mortality rate at 5-year follow-up was 29.4%. In addition, while the TTR rate was 40% in the general population, it was 49% in the low-intermediate risk group and 40% in the high-risk group (Table 3).

The most common oral anticoagulant treatment was warfarin (31.2%), followed by rivaroxaban (24.6%), dabigatran (15.9%), apixaban (11.8%), and edoxaban (1.8%), respectively. Seven hundred nine (27.4%) patients were not receiving any anticoagulant treatment. The death occurred in 251 patients (35.4%), an ischemic cerebrovascular event occurred in

Table 1. Demographic Characteristics and Echocardiographic Results

| CHA2DS2-VASc Score Risk Classification | Low-Medium Risk (n = 349) | High Risk (n = 2243) | P | Total (n = 2592) |
|--|---------------------------|----------------------|-------|------------------|
| Gender (female), n (%) | 105 (30.1) | 1333 (59.4) | <.001 | 1438 (55.5) |
| Age (years) | 56.2 ± 11.6 | 70.5 ± 9.4 | <.001 | 68.7 ± 11.1 |
| Body mass index (kg/m ²) | 27.9 ± 3.6 | 28.2 ± 4.0 | .135 | 28.2 ± 3.9 |
| Heart rate (minute) | 85.7 ± 17.7 | 87.9 ± 18.2 | .035 | 87.6 ± 18.2 |
| Systolic blood pressure (mm Hg) | 124.5 ± 15.2 | 128.5 ± 17.6 | <.001 | 128 ± 17.4 |
| Diastolic blood pressure | 76.3 ± 10.0 | 77.9 ± 11.6 | .014 | 77.7 ± 11.4 |
| Ischemic CMP, n (%) | 29 (8.3) | 644 (28.7) | <.001 | 673 (26) |
| Dilated CMP, n (%) | 11 (3.2) | 123 (5.5) | .067 | 134 (5.2) |
| Hypertrophic CMP, n (%) | 2 (0.6) | 18 (0.8) | .649 | 20 (0.8) |
| COPD, n (%) | 35 (10) | 417 (18.6) | <.001 | 452 (17.4) |
| DVT, n (%) | 0 | 6 (0.3) | .420 | 6 (0.2) |
| PE, n (%) | 1 (0.3) | 13 (0.6) | .419 | 14 (0.5) |
| Thyroid dysfunction, n (%) | 13 (3.7) | 77 (3.4) | .782 | 90 (3.5) |
| GFR (mL/min) | 58.4 (42.8-94) | 41.0 (28.5-64.8) | <.001 | 43.8 (29.9-68) |
| CRF, n (%) | 180 (51.6) | 1609 (71.7) | <.001 | 1789 (69) |
| Smoker, n (%) | 37 (10.6) | 114 (5.1) | <.001 | 151 (5.8) |
| HT, n (%) | 79 (22.6) | 1620 (72.2) | <.001 | 1699 (65.5) |
| DM, n (%) | 16 (4.6) | 560 (25) | <.001 | 576 (22.2) |
| Ischemic CVD/TIA, n (%) | 4 (1.1) | 204 (9.1) | <.001 | 208 (8) |
| Hemorrhagic CVD, n (%) | 3 (0.9) | 19 (0.8) | .585 | 22 (0.8) |
| EF (%) | 55.5 ± 7.8 | 49.8 ± 10.9 | <.001 | 50.5 ± 10.7 |
| LA diameter | 41.8 ± 6.6 | 45.4 ± 6.8 | <.001 | 44.9 ± 6.9 |
| LA volume | 62.9 ± 33.9 | 71.6 ± 31.3 | <.001 | 70.5 ± 31.8 |
| LA thrombus, n (%) | 8 (2.3) | 16 (0.7) | .004 | 24 (0.9) |

P value of <.05 shows statistical significance.

CMP, cardiomyopathy; COPD, chronic obstructive pulmonary disease; DVT, deep venous thrombus; PE, pulmonary embolism; GFR, glomerular filtration rate; CRF, chronic renal failure; HT, hypertension; DM, diabetes mellitus; CVD, cerebrovascular disease; TIA, transient ischemic attack; EF, ejection fraction; LA, left atrium.

Table 2. Results Obtained According to Atrial Fibrillation Classification and Management

| CHA2DS2-VASc Score Risk Classification | | Low-Medium Risk (n = 349) | High Risk (n = 2243) | P | Total (n = 2592) |
|--|-----------------------|---------------------------|----------------------|-------|------------------|
| AF type, n (%) | Lone AF | 53 (15.2) | 112 (5) | <.001 | 165 (6.4) |
| | Paroxysmal AF | 124 (35.5) | 386 (17.2) | | 510 (19.7) |
| | Persistent AF | 38 (10.9) | 215 (9.6) | | 253 (9.8) |
| | Permanent AF | 134 (38.4) | 1530 (68.2) | | 1664 (64.2) |
| EHRA classification | EHRA 1 | 129 (37) | 475 (21.2) | <.001 | 604 (23.3) |
| | EHRA 2 | 172 (49.3) | 1325 (59.1) | | 1497 (57.8) |
| | EHRA 3 | 47 (13.5) | 431 (19.2) | | 478 (18.4) |
| | EHRA 4 | 1 (0.3) | 12 (0.5) | | 13 (0.5) |
| AF treatment management, n (%) | Rate control strategy | 255 (73.1) | 1708 (76.1) | .212 | 1963 (75.7) |

P value of <.05 shows statistical significance.

AF, atrial fibrillation; EHRA, European Heart Rhythm Association.

44 patients (6.2%), and hemorrhagic stroke occurred in 2 patients (0.3%) during the 5-year follow-up period (Table 4). Switch ratios between warfarin and NOAC are given in Table 4.

Beta-blockers (65.1%) were the most common drugs used by the patients, followed by diuretics (40.7%), angiotensi-

n-converting enzyme inhibitors (29.9%), acetylsalicylic acid (29.1%), and angiotensin-II receptor blocker (24.1%) group drugs (Table 5). The results of the hemogram and biochemical parameters of the patients are summarized in Table 6.

The predictors of 1-year and 5-year mortality are shown in Figure 1 and Figure 2 in Cox regression models.

Table 3. Follow-up Results, HASBLED Score, and TTR Results

| CHA2DS2-VASc Score Risk Classification | Low-Medium Risk (n = 349) | High Risk (n = 2243) | P | Total (n = 2592) |
|--|---------------------------|----------------------|-------|------------------|
| Follow-up time (day) | 2072 (1197-2188) | 1626 (880-2130) | <.001 | 1920 (939-2133) |
| Ischemic CVD/TIA in follow-up, n (%) | 6 (1.7) | 136 (6.1) | .001 | 14(5.5) |
| Hemorrhagic CVD in follow-up, n (%) | 1 (0.3) | 11 (0.5) | .505 | 12 (0.5) |
| Death at first-year follow-up, n (%) | 6 (1.7) | 231 (10.3) | <.001 | 237 (9.1) |
| Death at fifth-year follow-up, n (%) | 36 (10.3) | 725 (32.3) | <.001 | 761 (29.4) |
| HASBLED score | 0 (0-1) | 2 (1-2) | <.001 | 1 (1-2) |
| TTR (%) | 49.0 (26-85.4) | 40 (22.8-70) | .163 | 40 (23-70) |

P value of <.05 shows statistical significance.

CVD, cerebrovascular disease; TIA, transient ischemic attack; TTR, time in therapeutic range.

Table 4. Oral Anticoagulation Treatment Use Results

| CHA2DS2-VASc Score Risk Classification | Low-Medium Risk (n = 349) | High risk (n = 2243) | Total (n = 2592) | P |
|--|---------------------------|----------------------|------------------|-------|
| Warfarin, n (%) | 84 (24.1) | 724 (32.4) | 808 (31.2) | .002 |
| Dabigatran, n (%) | 45 (12.9) | 367 (16.4) | 412(15.9) | .002 |
| Rivaroxaban, n (%) | 58 (16.6) | 579 (25.8) | 667(24.6) | .001 |
| Apixaban, n(%) | 36(10.3) | 271(12.1) | 307(11.8) | .078 |
| Edoxaban, n(%) | 3(0.9) | 44(2.0) | 47(1.8) | .151 |
| Anticoagulants | 198(56.7) | 1685(75.1) | 1883(72.6) | <.001 |
| Nonanticoagulants | 151(43.3) | 558(24.9) | 709(27.4) | |
| Switch Warfarin to NOAC, n (%) | 33(9.5) | 374(16.7) | 407(15.7) | .001 |
| Switch NOAC to Warfarin, n (%) | 1(0.3) | 16(0.7) | 17(0.7) | .311 |
| Switch NOAC to other NOAC, n (%) | 16(4.6) | 128(5.7) | 144(5.6) | .395 |

P value of <.05 shows statistical significance.

NOAC, new oral anticoagulant.

Table 5. Other Drugs Used by Patients

| | |
|----------------------|-------------|
| ASA, n (%) | 755 (29.1) |
| Clopidogrel, n (%) | 208 (8) |
| Prasugrel, n (%) | 2 (0.1) |
| Ticagrelor, n (%) | 1(0.0003) |
| Beta blocker, n (%) | 1687 (65.1) |
| Diltiazem, n (%) | 436 (16.8) |
| Verapamil, n (%) | 38 (1.5) |
| Digoxin, n (%) | 501 (19.3) |
| Amiodarone, n (%) | 114 (4.4) |
| Propafenone, n (%) | 86 (3.3) |
| Sotalol, n (%) | 17 (0.7) |
| ACE Inh., n (%) | 774 (29.9) |
| ARB, n (%) | 625 (24.1) |
| DHP-CCB, n (%) | 248 (9.6) |
| Statin, n (%) | 439 (16.9) |
| Diuretic, n (%) | 1054 (40.7) |
| Nitrate, n (%) | 144 (5.6) |
| Alpha blocker, n (%) | 47 (1.8) |
| PPI, n (%) | 449 (17.3) |

ASA, acetyl salicylic acid; ACE Inh., angiotensin-converting enzyme; ARB, angiotensin-II receptor blocker; DHP-CCB, dihydro pyridine-calcium channel blocker; PPI, proton pump inhibitor.

Kaplan–Meier analysis was performed to examine the survival time during 5 years of follow-up according to their CHA2DS2-VASc risk score classifications. As the risk class increased, lower survival rates were observed during the follow-up period (log-rank: 68.6; $P < .001$) (Figure 3). Additionally, the risk of ischemic CVD/TIA, hemorrhagic CVD, first-year death rate, and 5-year death rate were significantly higher in high-risk groups than in medium- and lower-risk groups as shown in Figure 4.

DISCUSSION

This multicenter, prospectively designed, epidemiological study was performed to investigate the frequency of oral anticoagulant drugs and TTR in patients receiving warfarin, and the prevalence of adverse events and mortality rates in addition to the epidemiological trial of NVAF previously conducted in Turkey (AFTER trial). Today, due to the increase in life expectancy and the increase in the frequency of comorbid diseases, the costs and expenses in the health sector have increased. Understanding the basic characteristics, risks, and frequency of treatment strategies, especially in AF patients in the whole population, may contribute to reducing these costs. In our study, the rate of female gender was higher, and most of them consisted of patients in the high-risk group. In the recent GARFIELD-AF study conducted in

Table 6. Hemogram and Biochemical Parameter Results

| CHA2DS2-VASc Score Risk Classification | Low-Medium Risk (n = 349) | High Risk (n = 2243) | Total (n = 2592) | P |
|--|---------------------------|----------------------|------------------|-------|
| Hg (gr/dL) | 13.8 ± 1.8 | 12.8 ± 1.8 | 13.0 ± 1.9 | <.001 |
| Hct (%) | 41.7 ± 4.8 | 39.6 ± 5.1 | 39.9 ± 5.1 | <.001 |
| Plt (10 ³ /μL) | 236 ± 70.4 | 235.5 ± 73.9 | 235 ± 70.9 | .914 |
| WBC, (10 ³ /μL) | 8.0 ± 2.5 | 7.9 ± 2.4 | 7.9 ± 2.4 | .416 |
| Neutrophil (%) | 59.8 ± 9.9 | 63.6 ± 10.3 | 63 ± 10.3 | <.001 |
| Lymphocyte (%) | 28.4 ± 8.9 | 25.4 ± 9.0 | 25.8 ± 9.0 | <.001 |
| Monocyte (%) | 7.2 ± 2.9 | 7.3 ± 2.7 | 7.3 ± 2.8 | .414 |
| MPV (%) | 9.0 ± 1.4 | 9.2 ± 1.5 | 9.2 ± 1.5 | .026 |
| Glucose (mg/dL) | 103.3 ± 22.7 | 120.7 ± 42.8 | 118 ± 41 | <.001 |
| Urea (mg/dL) | 29.1 ± 12.2 | 33.8 ± 15.6 | 33 ± 15.3 | <.001 |
| Creatinine (mg/dL) | 0.81 (0.71-1.0) | 0.9 (0.74-1.1) | 0.9 (0.74-1.1) | <.001 |
| ALT (U/L) | 19 (15-26) | 18 (13-25) | 18 (13-25) | <.001 |
| AST (U/L) | 22 (17-30) | 21 (17-28) | 21 (17-28) | .026 |
| Albumin (gr/dL) | 4.1 ± 0.5 | 4.0 ± 0.5 | 4.0 ± 0.5 | .092 |
| Total cholesterol (mg/dL) | 177.6 ± 42.2 | 179.4 ± 43.9 | 179 ± 43.7 | .474 |
| Triglyceride (mg/dL) | 135.3 ± 66.6 | 131.5 ± 61.6 | 132 ± 62.3 | .288 |
| LDL (mg/dL) | 110 ± 38 | 108.8 ± 35.2 | 109 ± 35.6 | .580 |
| HDL (mg/dL) | 42.8 ± 10.6 | 44.2 ± 12.2 | 44 ± 12.0 | .051 |
| Uric acid (mg/dL) | 6 (4.8-7) | 6.1 (5.1-7.5) | 6.1 (5.0-7.4) | <.001 |

P value of <.05 shows statistical significance.

Hg, hemoglobin; Hct, hematocrit; Plt, platelet; WBC, white blood cell; MPV, mean platelet volume; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

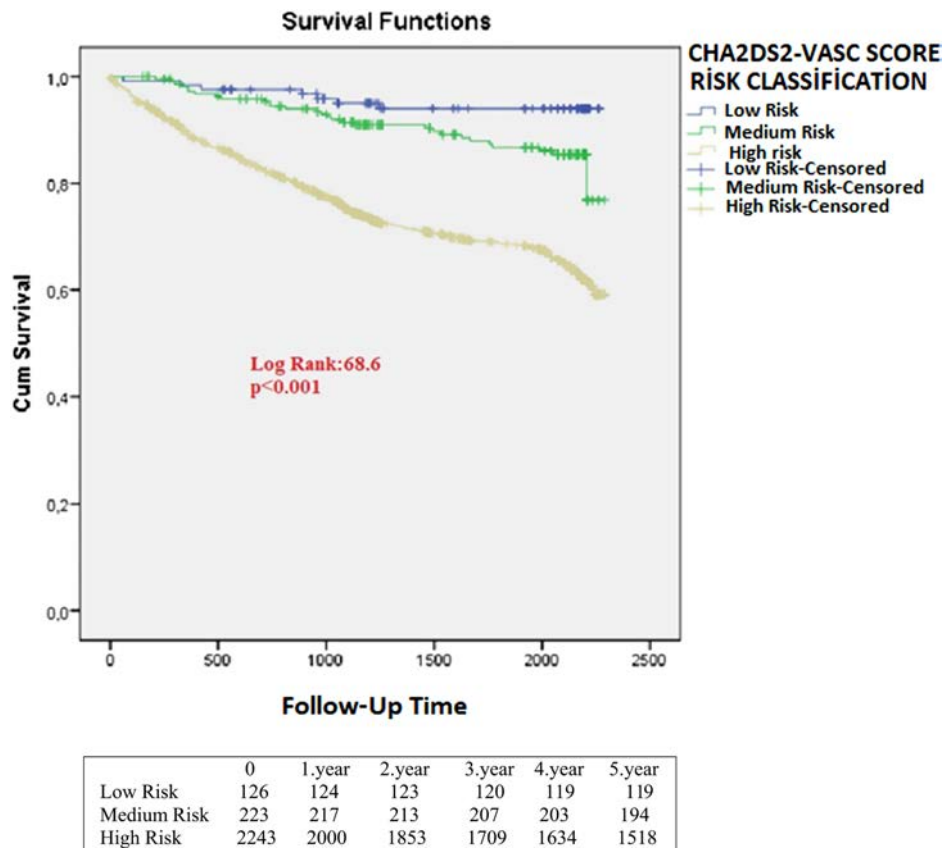


Figure 3. Kaplan–Meier analysis between CHA2DS2-VASc score risk classification and mortality during 5-year follow-up.

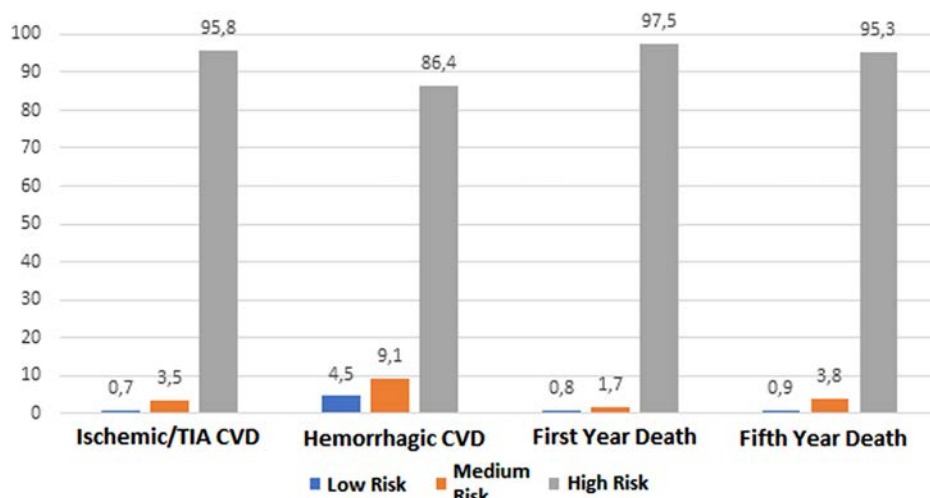


Figure 4. Relationship between primary endpoints and CHA2DS2-VASc score risk classification.

Turkey, it has been reported that the frequency of NVAF is higher in women.³ In addition, it was thought to be associated with obesity, metabolic syndrome, and cardiovascular diseases in Turkish women over 40 years of age.³ Similarly, the female sex ratio was higher in NVAF patients in the previous AFTER study.⁴ These findings were consistent with the results of our study. The majority of the patient population included in the study consisted of the high-risk group. In this respect, the distribution of patients in the low- and high-risk groups and the mean age were similar to the previous AFTER study.⁴ The mean age of NVAF patients was similar to previously conducted randomized controlled or observational trials. Chronic renal failure was found to be the most common comorbid disease because of elderly age and female gender. In our study, the most common comorbid condition with CRF was HT. In their study, Lip et al⁹ (the person who brought the CHA2DS2-VASc risk score to the literature) reported that the most common comorbid disease in AF was HT. The EORP-AF Pilot study indicated that asymptomatic atrial fibrillation is common in daily cardiology practice and is associated with elderly age, more comorbidities, and high thromboembolic risks. Higher 1-year mortality was found in asymptomatic patients compared with symptomatic patients.¹⁰ In the RAMSES study carried out by Başaran et al¹¹ it was reported that 72% of NVAF patients received anticoagulation treatment. In this study, NOAC use was more common than warfarin use. In our study, we found a slightly higher rate of use of anticoagulation therapy, especially with NOAC being more common. In addition, in the RAMSES study conducted at the same time as our study, similar results were obtained in terms of other demographic data and comorbid characteristics.¹¹ Among our patient population, rivaroxaban was the most commonly used NOAC, followed by dabigatran. These molecules were included in the scope of reimbursement earlier in our country. We think this is an influential factor. Dabigatran has been included in the scope of reimbursement since May 2013, and rivaroxaban has been included in the scope of reimbursement since October 2013.¹¹ In addition, we think that the single-dose use of rivaroxaban may be effective in the choice of treatment. It is known that reducing the dosage

frequency increases drug compliance. Pan et al¹² showed that choosing fixed-dose combination therapy can provide significant improvements in patient compliance compared to the choice of 2-drug therapy. In another study involving 10 697 patients with AF, it was shown that choosing a single dose of antidiabetic, antihypertensive, calcium channel blocker, and diuretic was advantageous compared to double-dose regimens in terms of drug compliance.¹³ Again, in some studies on NOACs, single-dose rivaroxaban regimen was superior to double-dose apixaban and dabigatran regimens in terms of drug compliance.^{14,15} In addition, the findings of the NOAC-TR study conducted in Turkey were also compatible in this respect.¹⁶ In the previous AFTER study, it was reported that an effective INR level was achieved in 37% of patients receiving warfarin treatment.⁴ A study conducted on the Turkish population by Basaran et al¹⁷ showed that ineffective use of warfarin treatment was 83% and the TTR rate was 40.5%. Another study conducted on the Turkish population showed that the TTR rate was 40.3% in NVAF patients.¹⁸ In our study, the TTR rate was 40%, which is compatible with these studies. The results of these national studies show us that the effectiveness of anticoagulation treatment with warfarin is relatively low. We can conclude that one of the reasons why NOACs are preferred to warfarin in Turkey is due to the low TTR ratios. The most preferred oral anticoagulant was warfarin in both ORBIT-AF and GARFIELD studies; on the contrary, the use of NOAC was more common than in warfarin in the GLORIA-AF study which is similar to our findings.¹⁹⁻²¹ In addition, according to the risk classification of the CHA2DS2-VASc score, approximately 9 out of 10 NVAF patients in our study required anticoagulation therapy; this result is consistent with previous studies.²² In our study, we found that age and gender, as well as comorbid conditions, had an effect on mortality. In this respect, we have revealed the factors that are independent predictors. In addition, we found that as the risk classification of the CHA2DS2-VASc score increased, the frequency of adverse events and mortality rates increased during the follow-up period. These findings supported previous studies in the literature.

Study Limitations

The study included only outpatients and did not include patients who were admitted to the emergency department or hospitalized. Therefore, the study did not include all AF patients but included a limited homogeneous patient population. However, consecutive patient data were obtained from all geographic regions in Turkey according to population density. The study protocol was not designed as a double-blind, so selection bias could not be excluded. The fact that the data obtained in this study were based on hospital records and patient information may have led to biased and inaccurate results. In addition, we could not identify patients using dual or triple antithrombotic drugs during patient follow-up. This may have influenced our primary endpoints. Since this study was designed nationally, the results cannot be generalized to data from other countries. In this respect, studies with wider participation are needed.

CONCLUSION

Our results draw an epidemiological perspective for NVAF patients in Turkey, including long-term follow-up results. It was revealed that most of the NVAF patients were in the high-risk group, and more than three-quarters of the patients received oral anticoagulation therapy. However, we can say that TTR rates are still low in Turkey, which is an important factor in increasing the transition from warfarin treatment to NOAC treatments. In addition, we would like to emphasize that our results in our study are important in terms of revealing the long-term adverse event and mortality rates in NVAF patients.

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Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Peer-review: Externally peer-reviewed.

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