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Predictors of warfarin use in patients with non-valvular atrial fibrillation who presented to the cardiology outpatient clinic of a tertiary hospital in Turkey: an observational study

Faruk ERTAŞ, Hasan KAYA, Zuhal ARITÜRK ATILGAN, Mehmet Ali ELBEY, Mesut AYDIN, Mehmet Ata AKIL, Mustafa OYLUMLU, Mehmet Sıddık ÜLGEN

Aim: The aim of this study was to investigate the predictors of warfarin use in patients with non-valvular atrial fibrillation (AF). This study was the first to be conducted in a Turkish population.

Materials and methods: Patients who presented to our outpatient clinic with the diagnosis of AF between September 2008 and October 2009 were enrolled. The patients were classified according to the CHADS2 risk scoring system recommended by the AHA/ACC/ESC guidelines for the classification of stroke risk in non-valvular AF patients. The probable variables influencing the use of warfarin were determined as age, sex, income level, healthcare coverage, lifestyle, place of residence, classification of AF, hypertension, diabetes mellitus, coronary artery disease, thyrotoxicosis, cardiac insufficiency, left ventricular dysfunction, stroke risk stratification, and history of stroke or systemic embolism (SE).

Results: Among the 570 patients enrolled in the study, 144 were excluded because of insufficient patient information or refusal to participate, while 101 patients were excluded due to valvular AF. Thus, the evaluation was based on 325 patients (133 males and 192 females; mean age: 65 ± 10). According to the CHADS2 scoring, 62.2% of the patients were at high risk, 26.8% were at moderate risk, and 11.1% were at low risk. Only 19.7% of the patients were on warfarin treatment. In the logistic regression analysis, a history of stroke or SE, high income level, and the presence of persistent and permanent AF were found to be positive predictors of warfarin use, while advanced age was a negative predictor of warfarin use.

Conclusion: This study demonstrated that a history of stroke or SE, high income level, presence of persistent and permanent AF, and advanced age are independent predictors of warfarin use in non-valvular AF patients.

Key words: Atrial fibrillation, warfarin, CHADS2, stroke, predictor

Introduction

Atrial fibrillation (AF) is a supraventricular tachyarrhythmia frequently observed in clinical practice and its prevalence increases with advancing age. Thromboembolic events constitute an important part of the morbidity and mortality associated with AF. Stroke is the leading thromboembolic event caused by AF (1–6), and the annual risk of stroke in these patients varies between 3% and 8% (7). Studies have shown that the most effective method in preventing this serious complication of AF is efficient anticoagulation achieved with warfarin (8). In a number of randomized and controlled studies, warfarin treatment at the target levels has been demonstrated to reduce the risk of stroke by two-thirds in patients with AF (9). Almost all the studies demonstrating the relationship between atrial fibrillation and warfarin treatment and evaluating the

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Department of Cardiology, Faculty of Medicine, Dicle University, Diyarbakır – TURKEY
Correspondence: *Hasan KAYA, Department of Cardiology, Faculty of Medicine, Dicle University, Diyarbakır – TURKEY*
E-mail: dr_hasankaya@yahoo.com

independent variables influencing the use of warfarin have been conducted on western populations. To date, no study has been conducted in this country focusing on the association between AF, which affects a major patient population and may lead to dramatic outcomes like thromboembolytic complications, and the predictors influencing the use of warfarin, which has a demonstrated efficiency in preventing these complications.

In the present study, our aim was to prospectively investigate the frequency and predictors of warfarin use in patients diagnosed with non-valvular AF according to the recommendations of the AHA/ACC/ESC AF guidelines. Since this study is the first to be based on a Turkish population, we are of the opinion that it will contribute to the literature in this country and pave the way for the future studies focusing on this point.

Materials and methods

Study population

The study group consisted of 570 consecutive patients who presented to our cardiology outpatient clinic with the diagnosis of AF between September 2008 and October 2009. Patients with prosthetic valves or a history of rheumatic valvular disease, those with contraindications against warfarin treatment, and patients who refused to participate in the study or supplied insufficient information were excluded. Each patient was given information about the purpose of the study and signed an informed consent form. The approval of the ethics committee was obtained before the start of the study. Patient information was obtained either from the patients or first-degree relatives.

Stroke risk stratification

Patients were classified according to the CHADS2 (congestive heart failure [CHF], hypertension [HT], age ≥75, diabetes mellitus [DM], and prior stroke or TIA) scoring system recommended by the AHA/ACC/ESC atrial fibrillation guidelines for the stratification of the risk in non-valvular AF.

Probable variables influencing warfarin use

From the medical records and the patient histories, the probable variables thought to influence warfarin use were specified as age, sex, income level, healthcare coverage, lifestyle, place of residence, classification of AF, HT, DM, coronary artery disease (CAD), thyrotoxicosis, cardiac insufficiency (CI), left ventricular (LV) dysfunction, stroke risk stratification, and history of stroke or systemic embolism (SE). In terms of the classification of AF, patients were grouped as those with paroxysmal or persistent/permanent AF. In terms of the stroke risk stratification, patients were divided into 3 categories as high risk, moderate risk, and low risk patients based on the CHADS2 scoring. The determination of the income level was based on the minimum wage during the years the study was conducted. The healthcare coverage of the patients was grouped in 4 categories according to the healthcare system in this country comprising the Green Card, Social Insurance Institution, State Retirement Fund, and the Social Security Organization of Artisans and Self-Employed Individuals. The lifestyle parameter was classified as those who live together with their families and those who live alone. The place of residence was described as the urban area at the center of the province the study was conducted in and the rural parts of the same province. Patients were also asked about any antiaggregant (aspirin) and/or anticoagulant (warfarin) treatments.

Electrocardiography/echocardiography

All the patients enrolled in the study underwent surface electrocardiography during the enrollment phase through a 12-lead electrocardiography device at a velocity of 25 mm/s and a calibration of 10 mm/mV. Moreover, in order to evaluate the LV functions of the patients, 2-dimensional M-mode echocardiographies were performed using a General Electric-Vivid 3 echocardiography device.

Statistical analysis

Statistical analyses were performed using SPSS (Statistical Package for the Social Sciences for Windows) 15.0 software. Numerical variables were evaluated through Student's t-test, while the categorical variables were compared using Pearson's chi-square test. A binary logistic regression analysis was performed to evaluate the independent predictive values of the potential variables of age, stroke, high income level, and classification of AF as predictors of warfarin use. Statistical significance was based on a value of $P < 0.05$.

Results

Among the 570 patients enrolled in the study, 144 were excluded because of insufficient patient information or refusal to participate, while 101 patients were excluded due to valvular AF. Thus, the evaluation was based on 325 patients (133 males [40.9%] and 192 females [59.1%]; mean age: 65 ± 10). The demographic and socioeconomic parameters of the patient groups on warfarin treatment and those who did not receive any warfarin treatment are presented in Tables 1 and 2. The sex, age distribution, and clinical risk factors of the patient groups were similar. Only the warfarin treatment rate in patients with a history of stroke or SE (P = 0.001) and in those with persistent/permanent AF (P = 0.024) was significantly higher. According to the CHADS2 score, 62.2% of the patients were in the high risk group, 26.8% were in the moderate risk group, and 11.1% were in the low risk group. However, no difference was observed between the groups in relation to warfarin use. While no difference between the groups was found in terms of the socioeconomic factors such as healthcare coverage, lifestyle, and place of residence, the rate of warfarin use was observed to increase with increasing level of income (P = 0.002).

The treatment modalities administered to the patients are presented in the Figure. Among the patients, 56 (17.2%) were on aspirin and warfarin, 8

Table 1. Comparison of the patients on warfarin treatment with those not on warfarin in terms of clinical risk factors.

Main features		Warfarin (–) (n = 261)	Warfarin (+) (n = 64)	P
		n (%)	n (%)	
Sex	Male	108 (81.2)	25 (18.8)	0.736
	Female	153 (79.7)	39 (20.3)	
Age	≤65	85 (75.2)	28 (24.8)	0.154
	66–74	72 (80.0)	18 (20.0)	
	≥75	104 (85.2)	18 (14.8)	
Hypertension	No	67 (82.7)	14 (17.3)	0.529
	Yes	194 (79.5)	50 (20.5)	
Coronary artery disease	No	189 (78.8)	51 (21.2)	0.235
	Yes	72 (84.7)	13 (15.3)	
Cardiac insufficiency	No	216 (80.9)	51 (19.1)	0.565
	Yes	45 (77.6)	13 (22.4)	
LV dysfunction (EF)	≤35%	41 (82.0)	9 (18.0)	0.744
	>35%	220 (80.0)	55 (20.0)	
Diabetes mellitus	No	220 (80.6)	53 (19.4)	0.772
	Yes	41 (78.8)	11 (21.2)	
History of stroke or systemic embolism	No	230 (83.3)	46 (16.7)	**0.001**
	Yes	31 (63.3)	18 (36.7)	
Thyrotoxicosis	No	246 (80.4)	60 (19.6)	0.878
	Yes	15 (78.9)	4 (21.1)	
AF classification	Persistent/permanent	165 (76.7)	50 (23.3)	**0.024**
	Paroxysmal	96 (87.3)	14 (12.7)	
Stroke risk stratification	Mild	31 (86.1)	5 (13.9)	0.311
	Moderate	73 (83.9)	14 (16.1)	
	High	157 (77.7)	45 (22.3)	

Table 2. Comparison of the patients on warfarin treatment with those not on warfarin in terms of socioeconomic parameters.

Socioeconomic factors		Warfarin (–)	Warfarin (+)	P
		n (%)	n (%)	
Income level	0–457 TL/month (Low)	136 (86.1)	22 (13.9)	**0.002**
	457–916 TL/month (Moderate)	108 (78.3)	30 (21.7)	
	>916 TL/month (High)	17 (58.6)	12 (41.4)	
Healthcare coverage	Green Card	60 (88.2)	8 (11.8)	0.299
	Social Insurance Institution	121 (78.6)	33 (21.4)	
	Social Security Organization of Artisans and Self-Employed Individuals	45 (76.3)	14 (23.7)	
	State Retirement Fund	29 (78.4)	8 (21.6)	
Lifestyle	With the family	231 (79.7)	59 (20.3)	0.395
	Alone	30 (85.7)	5 (14.3)	
Place of residence	Urban	185 (79.4)	48 (20.6)	0.512
	Rural	76 (82.6)	16 (17.4)	

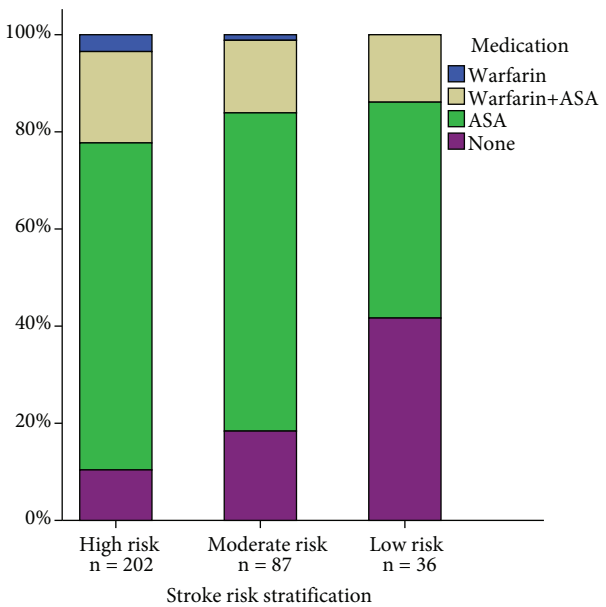

Figure. Distribution of treatment used according to the risk classification.

(2.5%) were only on warfarin, and 209 (64.3%) were treated only with aspirin. The remaining 52 (16%) patients were not on any of these treatment options. From the point of view of the stroke risk category, the rate of warfarin treatment in the high and moderate risk groups was 22.3% and 16.1%, respectively. Approximately one-tenth (10.4%) of the patients in the high risk group and one-fourth of the patients in the moderate risk group (26.8%) had not received any of the warfarin and/or aspirin treatment modalities.

In the binary logistic regression analysis where the factors affecting warfarin use were evaluated, persistent/permanent AF, history of stroke or SE, and high income level were found to be positive predictors of warfarin use, while advanced age was found to be a negative predictor (Table 3).

Discussion

This study demonstrates that although it is known that the most efficient method to prevent an important

Table 3. Predictors of warfarin use in the multivariate regression analysis.

Clinical variables	Odds ratio	95% Confidence interval	P-value
Advanced age (>75)	0.410	0.201–0.835	**0.014**
Persistent/permanent AF	2.109	1.043–4.263	**0.038**
History of stroke or systemic embolism	2.912	1.418–5.979	**0.004**
High income level	4.338	1.757–10.711	**0.001**

complication like ischemic cerebrovascular diseases that develop secondary to AF is effective anticoagulation provided by warfarin, AF patients in this country do not receive adequate anticoagulative treatment through warfarin in spite of the observed indication. Furthermore, this study has indicated that a history of stroke or SE, high income level, and persistent/permanent AF are positive predictors of warfarin use in patients with AF, while advanced age is a negative predictor.

Several previous studies have demonstrated that treatment with oral anticoagulants is effective in preventing strokes and deaths related to thromboembolism in patients with non-valvular AF (10–15). The first large-scale study providing data on oral anticoagulant treatment in patients with AF was by Stafford and Singer (16). Warfarin treatment was also previously studied in the Atrial Fibrillation, Aspirin and Anticoagulation (17), Stroke Prevention in Atrial Fibrillation (18–20), Boston Area Anticoagulation Trial for Atrial Fibrillation (21), Canadian Atrial Fibrillation Anticoagulation (22), and Stroke Prevention in Nonrheumatic Atrial Fibrillation (23) studies. When the results obtained from these studies were examined in light of the guidelines, a drastic increase was observed in the number of the AF patients who received warfarin treatment (10).

The most interesting studies on the predictors of warfarin use in non-valvular AF patients are those by Go et al. (12). Other investigators analyzed the positive and negative predictors of warfarin use in non-valvular AF patients (24–27). These studies revealed that a history of stroke or SE and advanced age are independent predictors of warfarin use (28). In parallel to these studies, also in our study, a history of stroke or SE and advanced age were observed to be independent predictors of warfarin use. However, although the frequency of AF and the related stroke risk increase in parallel with age, advanced age in our study turned out to be an unexpected negative predictor of warfarin use. We attributed this result to the concerns of the physicians in this country related to increased bleeding risk in the elderly. Moreover, in the study by Go et al., socioeconomic factors (such as income level, healthcare coverage, and lifestyle) and place of residence (like urban or rural areas) directly influencing the patients' living conditions were not evaluated. Our study revealed that high income level is a positive predictor of warfarin use, and, to the best of our knowledge, this point was not investigated in the literature before. As the income level increases, the individuals' health knowledge and their tendency to seek health assistance increase in parallel. However, lifestyle and the place of residence were observed to be unrelated to oral anticoagulant treatment. It was especially surprising that the place of residence did not have any influence on oral anticoagulant treatment, since the general idea is that oral anticoagulant use is rarer in patients living in rural areas since the prothrombin time cannot be checked frequently enough. The results we observed may be related to the increase in the number and equipment of the health centers in rural areas and in the awareness of the patients in terms of cardiovascular health in recent years.

Furthermore, except for the study by Waldo et al. focusing on the predictors of oral anticoagulant therapy (29), the classification of AF has not been investigated as a predictor of warfarin use. It was Waldo et al. who first suggested that persistent/permanent AF was a positive predictor of warfarin use (29). In agreement with their study, in our study the presence of persistent/permanent AF was also shown

to be a positive predictor of warfarin use. To the best of our knowledge, this is the second study evaluating this point. Although patients with paroxysmal AF are at similar risk of stroke as persistent/permanent AF patients, it is surprising that warfarin use is less common in these patients. This may be associated with both the physicians' inadequate awareness of paroxysmal AF and the fact that the patients regard this situation as a transient disorder and are unwilling to undergo a distressing process involving frequent prothrombin time checks.

Interestingly enough, high risk of stroke was not revealed to be an independent predictor for warfarin use in spite of the slight tendency observed. Similarly, in a study by McCormick et al. (30) conducted in long-term care patients, as the number of the risk factors for stroke increased, warfarin use also showed an increasing trend, although this increase was statistically insignificant. Data obtained from the recent studies focusing on the subject also support this point (31,32). The results of both studies show that the stroke risk stratification is not paid due attention by physicians and patients are not adequately warned about this point.

In our study, 22.3% and 16.1% of the patients in the high and moderate risk categories for stroke received oral anticoagulant therapy, respectively. Although the ACC/AHA/ESC joint guidelines recommend aspirin treatment in addition to warfarin for the group at moderate risk of stroke, only 14.9% of the patients in the moderate risk group in our study had received aspirin and warfarin in combination. In addition, while the guidelines recommend only aspirin treatment for the group at mild risk of stroke, 13.9% of these patients in our study had received treatment with the combination of aspirin and warfarin. These results indicate that oral anticoagulant treatment is not administered appropriately even in tertiary hospitals in this country.

Since nearly all of the studies to date focusing on the use of warfarin in AF patients have been conducted on western populations, the obtained results may show important differences from the Turkish population. As our study is the first to be conducted on this particular subject in this country, we are of the opinion that our results reveal the real characteristics of our society. For instance, previous large-scale AF studies have indicated that age is a primary predictor for AF. The ACC/AHA/ESC guidelines developed based on these studies mostly conducted in western societies consider age of 75 and above as a moderate risk factor and age of 65 and above as a mild risk factor for stroke. It is known that the average life expectancy in our society is lower than that in western societies. Indeed, the majority of the AF patients in our study were aged 65 years or above, and their mean age was 65. For this reason, drawing the line for the moderate risk factor at >65 years instead of >75 years may be considered when the risk factors for ischemic stroke in the AF patients in this country are determined.

The majority of the AF patients who presented to the cardiology outpatient clinic of our hospital were at high risk for ischemic stroke. In spite of the studies that may be considered milestones in showing the importance of oral anticoagulant therapy in preventing strokes, only one-fifth (22.3%) of the patients at high risk of stroke were receiving treatment with oral anticoagulants. In this study reflecting daily clinical practice, it is obvious that the inadequate use of oral anticoagulant treatment modalities cannot be explained just by medical contraindications. We are of the opinion that the most important factor leading to inadequate oral anticoagulant therapy is the inadequate prescription by the physicians. The observed lack of oral anticoagulant therapy reveals that the guidelines are not efficiently reflected in clinical practice. A possible reason for this may be the fact that the majority of physicians organizing the treatment for AF are not cardiologists. Moreover, the majority of the physicians are not sufficiently informed about AF and its risks, and are hesitant about prescribing oral anticoagulant treatment. These factors consequently tip the scale against the oral anticoagulant therapy in terms of the risk/benefit ratio.

In conclusion, we have demonstrated in this study that the presence of persistent/permanent AF, a history of stroke or SE, and high income levels are positive independent predictors for warfarin use, while advanced age is a negative independent predictor. In this respect, awareness programs are needed for both the physicians and the patients with low income status, with paroxysmal AF, or at high risk for stroke and not on adequate warfarin treatment.

Since the present study is the first to be conducted in the Turkish population, we are of the opinion that it will contribute to the literature in this country and pave the way for future studies focusing on this point, so that the health community gains awareness of AF patients, constituting a considerable patient population in this country.

Limitations of the study

The main limitation of this cross-sectional study was the limited number of study subjects.

This was a single-center study; therefore, its results may not be generalized to other clinical settings. Another limitation is the lack of HAS-BLED and CHADS-VASc scores. A final limitation of our study is that the patients were evaluated in a single visit and no follow-up visits were conducted.

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