Identification of Risk Scores in Patients Using Warfarin and Evaluation of Initiation Rates with Accurate Indications

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ABSTRACT

Objective: More detailed observation of deciding to provide thromboembolic prophylaxis which is the most important complication for patients with artrial fibrillation and choosing right agent.

Methods: Totally 300 patients who were under warfarin treatment with nonvalvuler AF diagnosis has been allocated in this study. The observation was hold to give correct anticoagulant therapy to eligible patients by evaluating patients by using CHA2DS2-VASC and HASBLED scoring systems and by calculating right indication and risk of bleeding calculation.

Results: When we evaluate CHA2DS2-VASC scores of participants, 0 was observed as the lowest risk score, 9 as the highest score and 3.4067±1.76967 as average risk level. HASBLED point of participants was obtained at 2.11±1.178 level. 66% of participants got (n=198) 2 or lower scores, 34% of them got n=102) 3 or over.

Conclusion: In this study, we showed that patients receiving warfarin treatment started to use the medicine with correct indications, but they were not sufficiently evaulated with regard to side effects of the drug. In patients without high bleeding risk factors, using warfarin prophylaxis of venous thromboembolism in the presence of endication is indisputable. It is keeping its importance among alternatives for both providing the strongest anticoagulation effect with warfarin treatment and cost reasons. Although the use of new oral anticoagulant drugs are recently being discussed as an alternative, we obtained a conclusion that treatment decision should be made after the evaluation of patient convenience for warfarin treatment, considering that side effects and antidotes of new medicines are not known and that new medicines are not known and that new medicines have higher cost. *(JAREM 2015; 5: 115-20)*

Keywords: Warfarin, atrial fibrillation, accurate indication

INTRODUCTION

Atrial fibrillation (AF) is most common type of cardiac arrhythmia and is seen in 1–2% of the general population (1). The incidence and prevalence of AF increases with age and reaches 8% in patients over 80 years old (2, 3). AF is an important public health problem due to its common occurrence and the frequent referrals and admissions to hospitals. AF is characterized by ECG recordings showing low-amplitude P waves and an irregular R-R distance accompanied by high-frequency atrial waves (350–600 / min) and a normal ventricular wave frequency (120–180 / min). The mortality rate of AF patients is two times greater than that of individuals with a normal sinus rhythm (3). Stroke, thromboembolism, heart failure, decline in quality of life, and cognitive impairment are the most important causes of morbidity and mortality in AF. Patients diagnosed with AF have a risk of ischemic stroke that is 4–5 times greater than that of the general population. Unfortunately, variability in the clinical picture of AF has prevented effective determination of the optimal treatment for this disorder (4). Deciding whether to start thromboembolism prophylaxis and determining the appropriate agent for this treatment are the most important steps in developing a treatment plan for AF patients. In patients with permanent AF diagnosis, the decision to begin thromboembolism prophylaxis should consider comorbid diseases and criteria, and if anticoagulation therapy is initiated, an appropriate agent must be used, taking the patient-specific risk factors into account.

In our study, we examined in 300 patients diagnosed with nonvalvular AF whether anticoagulation therapy was appropriately started and whether treatment options were sufficiently assessed through risk calculations. Our aim was to examine in detail the decision-making process used when determining whether to provide thromboembolic prophylaxis, the most common source of complication in patients with AF, and to assess the suitability of the agent selected. Specifically, we assessed how often risk scores had been evaluated in patients using warfarin and how often the drug had been started appropriately.

METHODS

Our study included 300 patients taking warfarin based on a diagnosis of non-valvular AF. In the patients evaluated by the CHA_2DS_2-VASC and HAS-BLED scoring systems, examinations were conducted to determine the appropriate anticoagulant treatment to be administered for each patient by making calculations of appropriate indications and bleeding risk. Participants

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were evaluated for 8 risk factors with reference to the risk tables of the CHA_2DS_2-VASC, and a total score was determined. Some risk factors were valued at 2 points: history of stroke, trans-ischemic attack, history of thromboembolism, and an age greater than 75 years. Others were valued at 1 point each. According to the HAS-BLED risk scale, participants were evaluated over 7 risk factors. Each patient was individually questioned during the polyclinic application to assess CHA_2DS_2-VASC and HAS-BLED scores, and then, using the calculated scores, determination was made as to whether each patient had received an appropriate treatment.

Patients under 18 years of age and those taking warfarin for a reason other than non-valvular AF were excluded.

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS) version 20 (IBM SPSS Statistics, NY, USA) was used for statistical analysis. In addition to descriptive statistical methods (mean, standard deviation, and frequency), the independent samples t-test was used for the comparison of quantitative data, and the Chi-square test was used for the comparison of qualitative data. The results were evaluated at a 95% confidence interval, and significance was set at $p<0.05$.

RESULTS

Of the 300 participants, 40.0% were female (n=120) and 60.0% were male (n=180). The age of the participants ranged from 35 to 97 years, and the average age was 66.14±10.64 years.

Additionally, 37.3% (n=112) of the participants were 65–74 years old, 57.3% (n=172) were primary school graduates, and 75.7% (n=227) were married (Table 1).

When the CHA_2DS_2-VASC scores were evaluated, the lowest risk score was 0 and highest risk score was 9, and the average level of risk was found to be 3.4067±1.76967.

Participants had the following CHA_2DS_2-VASC risk factors: 77.3% had hypertension (n=231); 42.3% had congestive heart failure (n=127); 40% were female (n=120); 37.3% were 56–74 years of age (n=112); 30.3% had vascular disease (n=91); 29.7% had diabetes mellitus (n=89); 23.3% were older than 75 years (n=70); and 18.7% had a history of stroke, trans-ischemic attack, or thromboembolism (n=56) (Table 2).

When CHA_2DS_2-VASC scores were considered for risk assessment, while 14.7% (n=44) of participants had a score of 1 point or lower, 85.3% (n=256) had scores of 2 or more points (Figure 1).

Participants had the following HAS-BLED risk factors: 77.7% had hypertension (n=233), 60% were older than 65 years, 24.3% had labile INR (n=73), 18.7% experienced stroke (n=56), 17.3% had used drugs or alcohol, 9.3% had bleeding (n=28), and 3% had abnormal liver or renal function (n=9) (Table 3).

The average HAS-BLED score of the participants was 2.11±1.178. The scores of the participants ranged from 0 to 6. While 66% of the participants (n=198) got 2 points or fewer, 34% (n=102) got 3 or more points (Figure 2).

DISCUSSION

We found that warfarin was started appropriately in patients in our study; however, the patients had not been not adequately assessed in terms of side-effects. Many large-scale studies have previously shown oral anticoagulant therapy to be highly effective in preventing thromboembolism-induced stroke and death in patients with AF (5, 6). Based on the results of these prior studies, guidelines on the use of oral anticoagulants in AF patients with a risk of stroke have been published and have gained wide acceptance (7, 8). However, due to possible highly detrimental side-effects of anticoagulant therapy, determining the bleeding risk profiles of patients prior to initiating treatment have been considered important and have placed restrictions on the treatment when following relevant guidelines.

In our study, we found that treatment had been started under the correct indications in patients using warfarin but that the treatment had been initiated without studying the risk of bleeding or thoroughly assessing drug options. Of the 300 patients, 85.3% got ≥2 points in the CHA_2DS_2-VASC scoring and, thus, had the appropriate indication to start thromboembolism prophylaxis. However, when they were individually assessed for the presence of risk factors of bleeding, 33.3% of them got ≥3 points in the HAS-BLED scoring, showing that use of other drugs for anticoagulation should have been attempted before warfarin.

The decision to begin prophylactic anticoagulation therapy, particularly in older patients, is very complex. Thorough assessment of thrombosis risk versus bleeding risk and selection of appropriate agents continue to be vital and intriguing issues. In elderly patients, key points to consider when determining whether to start anticoagulation treatment include cognitive status of the patient, continuity of access to medication, provision of a regular control of the anticoagulation parameters in

Table 1. Frequency distribution of age, marital status, and education

		n	%
Age (years)	54 and below	42	14.0
	Between 55 and 64	76	25.3
	Between 65 and 74	112	37.3
	Between 75 and 84	59	19.7
	85 and over	11	3.7
Education	No education	86	28.7
	Primary school	172	57.3
	Secondary school	22	7.3
	High school and higher	20	6.7
Marital Status	Married	227	75.7
	Single	6	2.0
	Widow	67	22.3

Table 2. CHA_2DS_2-VASC risk distribution

Risk factor		n	%
C- Congestive heart failure (or left ventricular dysfunction)	No	173	57.7
	Yes	127	42.3
H- Hypertension (systolic blood pressure≥140/90 mmHg or hypertension brought under control with medications)	No	69	23.3
	Yes	231	77.3
A_2 -Age ≥75 years	No	230	66.7
	Yes	70	23.3
D- Diabetes Mellitus	No	211	70.3
	Yes	89	29.7
S_2- Previously experienced stroke, trans-ischemic attack, or a history of thromboembolism	No	244	81.3
	Yes	56	18.7
V- Vascular disease (such as peripheral arterial disease, myocardial ischemia, aortic plaque)	No	209	69.7
	Yes	91	30.3
A- Age between 65 and 74 years	No	188	62.7
	Yes	112	37.3
Sc- Female gender	No	180	60.0
	Yes	120	40.0

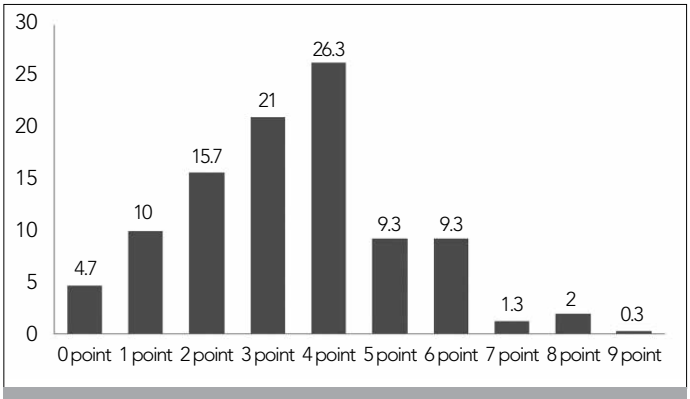

Figure 1. Percentage of the total scores of CHA_2DS_2-VASC

outpatients, and adjustment of the dose of warfarin or low-molecular-weight heparin.

Clinicians experience difficulty when deciding whether to start anticoagulation therapy, particularly in elderly patients even if they have appropriate indications. Patients are often unable to receive necessary thromboembolism prophylaxis due to difficulties in patient monitoring, particularly with those living in rural areas and in those who have recurrent falls, cognitive impairment, a history of gastrointestinal system bleeding, hypertension, cerebral hemorrhage, or a risk of adverse drug interactions. On study determined that the factors with the highest risk

Table 3. HAS-BLED risk distributions

Risk factor		n	%
H- Hypertension	No	67	22.3
	Yes	233	77.7
A- Abnormal liver and kidney function (1 point each)	No	291	97.0
	Yes	9	3.0
S- Stroke	No	244	81.3
	Yes	56	18.7
B- Bleeding	No	272	90.7
	Yes	28	9.3
L- Labile INRs	No	227	75.7
	Yes	73	24.3
E- Age (e.g., ≥65 years)	No	118	39.3
	Yes	182	60.7
D- Drugs or alcohol (1 point each)	No	248	82.7
	Yes	52	17.3

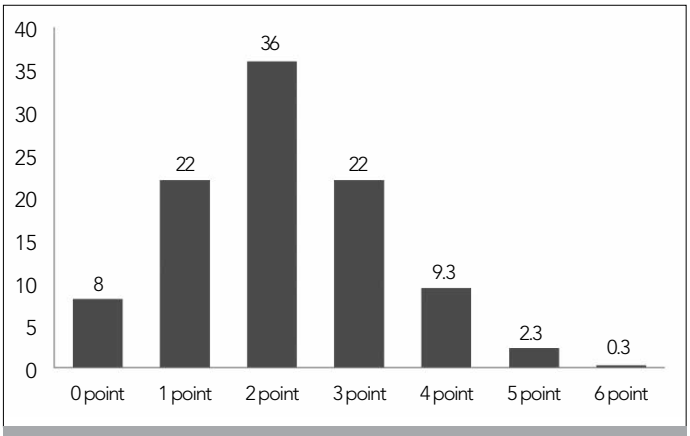

Figure 2. Percentage of the total scores of HAS-BLED

are patients who have insufficient information about the drug, a history of using more than 7 different drugs, and an INR above the target value (≥3) (9). Our study showed that a high rate of anticoagulant therapy can be initiated in patients with an indication. Of note, the patients in our study were treated at a large central hospital and there were no difficulties in monitoring patients living in rural areas or in patients gaining accessing to physicians; these facts likely played a role in the outcome of our study.

In this study, we assessed the appropriateness of the decision to start anticoagulation therapy in elderly patients. First, whether the patient needs thromboembolism prophylaxis should be determined; the CHA_2DS_2-VASC scoring system has been identified as the most appropriate means by which to accomplish this task (10). A meta-analysis of 29 randomized studies has shown that the relative abilities of warfarin and aspirin to prevent stroke are similar (11). However, warfarin was found to be stron-

ger than aspirin in one study: the Birmingham Atrial Fibrillation Treatment of the Aged (12). The ACTIVE study showed that the combined use of aspirin–clopidogrel lagged behind warfarin in its ability to prevent ischemic stroke. However, it has also been shown that combined aspirin–clopidogrel treatment has a risk of major bleeding that is equal to that of warfarin. Further, that same study stated that the risk of major bleeding in patients should be determined prior to initiation of treatment (13). The proposed scoring systems for determination of major bleeding risk are the ATRIA and the HAS-BLED scoring systems. Patients who are at a high risk of bleeding should be carefully evaluated for use of anticoagulant therapies other than warfarin. Another problem in elderly patients on warfarin treatment is drug–drug interactions or variability in INRs of patients after dietary changes. As age increases, an increasing tendency of bleeding has been observed in patients taking anticoagulant therapy as part of a treatment regimen for AF. According to one study, the typical average dose of warfarin at 5 mg/day has been shown to cause overdose in 82% of women and 65% of men. Therefore, warfarin treatment should be initiated at lower doses. The variability in patient response to warfarin dosage is due to vastly differing contributions of the CYP2C9 and VKORC1 enzyme variants in different patients. Unfortunately, performing a test to determine the different patient risks to higher dosages of warfarin before treatment is not recommended because it is not cost effective. Maintaining warfarin dosage in the therapeutic range is difficult because elderly patients have frequent changes in medication and diet due to other diseases. For all of these reasons, initiation of warfarin treatment is not recommended in elderly patients even when they have a thromboembolism prophylaxis indication if they also have a history of dementia, live alone, or do not have family support which negatively impacts the frequent monitoring requirements.

Falling tendency in patients should not be considered an absolute contraindication for the use of warfarin because the risk of intracranial hemorrhage due to falling was too low compared with the benefit achieved by reducing the risk thromboembolism. The risk of falling in elderly patients seems to be a common reason clinicians fear starting warfarin treatment. However, the OALY study showed that a person taking warfarin for AF would have to fall 295 times in a year for the risk of intracranial hemorrhage due to outweigh the benefits of reducing thromboembolism.

In our study, 85.3% of the patients received treatment appropriately according to their CHA_2DS_2-VASC scoring. We believe that this result, which is far above the average of our country, was due to the selection of a cardiology clinic at a major educational and research hospital that specializes in cardiovascular diseases, even though this clinic provides service to a heterogeneous patient population. This is one of the limitations of our study, as it is not representational of the country as a whole. The current situation in Turkey could be more broadly determined in an additional study by selecting centers containing different specialties (such as neurology, internal medicine, family medicine outpatient clinics).

We found that 34% of the patients who participated in our study got 3 or more points on their HAS-BLED score, which assess the risk of bleeding. The subset of this patient group who also got 2 or more points on their CHA_2DS_2-VASC score (approximately 33.3% of the patients) should be evaluated for compliance with other anticoagulant treatment options instead of warfarin. Despite the pertinent specialization of the specific center where our study was conducted, warfarin treatment was started in these patients without adequate assessment of other treatment options for at-risk patients.

Prior to making a treatment decision, doctors should determine whether a patient is in the high-risk group for thromboembolism according to the CHA_2DS_2-VASC scoring, and afterwards, their risk of bleeding should be calculated. HAS-BLED seems to be the most appropriate scoring system under the current circumstances. However, in large part due to variable sensitivity in elderly patients, it would be appropriate to add "phenotype fragility" and polypharmacy to the scoring systems. Few algorithms take function, cognition, social support, and fragility into account in the elderly population. Age alone is not a cause for contraindication in terms of anticoagulation because not all patients are at the same level of cognition and fragility. Contrary to popular belief, it has been found that number of decisions made to initiate anticoagulation therapy increase as physicians consider each case on more individualized bases.

The CARAT scoring system, which was recently used to individualize treatment, was also applied to the patients in our study. Thromboembolism prophylaxis indication was found in 33.3% of the patients who got 2 or more points in the CHA_2DS_2-VASC scoring system, and these patients were also included in the high-risk group in terms of bleeding risk by getting 3 or more points in the HAS-BLED scoring system. Care should be given during the treatment process for this group of patients for whom the appropriate approach is unclear. Anticoagulant therapy must be started in these patients. However, the use of aspirin, clopidogrel, or new oral anticoagulant drugs before warfarin treatment would be more appropriate because of the high risk of bleeding with warfarin. The choice among these drugs is completely based on the individual, and the suitability of each of these drugs has not been fully assessed to date. The easiest patients to treat are those who got 2 or more points in the CHA_2DS_2-VASC scoring system and who were not included in the high-risk group in terms of bleeding according to the HAS-BLED scoring system. However, to avoid the side-effects of warfarin, new oral anticoagulant drugs (such as dabigatran and apixaban) are recommended for these patients as well. Even though the new oral anticoagulant drugs seem to be at the forefront in recent studies (ROCKET and RELY), many questions remain unanswered (14, 15). For warfarin to be considered as a long-term anticoagulation therapy, several factors must be taken into account: INR measurement, multidrug interactions, the narrow therapeutic range of warfarin and its side-effects in the long run, and the presence of an effective and low cost alternative.

The characteristics of the new oral anticoagulants can be summarized as follows: no need of follow-up with periodic laboratory tests, less drug interaction, unknown long-term side-effects, usage twice per day, high cost, and lack of antidotes.

Anticoagulant therapy should be individually determined for each patient after the benefit is clearly identified. However, more comprehensive and long-term studies are needed to clarify the controversial points.

CONCLUSION

In our study, we evaluated whether AF patients were appropriately assessed in terms of suitability for anticoagulant treatment options. This study was performed considering the prejudices in both patients and physicians due to difficulties in monitoring warfarin treatment and the need for a better determination of the most suitable treatment option by evaluating newly introduced anticoagulant drugs. From the results of our study, it was seen that patients took thromboembolism prophylaxis with appropriate indications. However, it was also seen that patients were not thoroughly assessed for the risk of bleeding and warfarin treatment was given to patients who were not good candidates to receive it. This situation may lead to the more common occurrence of warfarin side-effects by providing unsuitable conditions and may cause unnecessary fears when physicians start warfarin treatment in new patients and may also side-effects due to accompanying risk factors in more patients. The need for use of warfarin is indisputable in patients who do not have high bleeding risk factors in thromboembolism prophylaxis with the presence of indications. According to studies, the most powerful anticoagulation is provided with warfarin treatment, and it is still important in treatment options because of its cost. New oral anticoagulant drugs are discussed as an alternative to warfarin treatment today; because of the fact that their side-effects and antidotes are unknown and their use is expensive, it was concluded that the treatment decision should be taken after the appropriateness of the patient is evaluated in terms of warfarin. Because of all these reasons, warfarin still has an important place in the existing anticoagulant treatments, despite the introduction of new oral anticoagulant drugs.

Ethics Committee Approval: Ethics committee approval was received for this study from Şişli Hamidiye Etfal Training and Research Hospital Local Ethical Comittee.

Informed Consent: Verbal informed consent was obtained from patients who participated in this study.

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Author Contributions: Concept - S.U., O.B.; Design - S.U., O.B.; Supervision - S.U., O.B., S.Y., N.D.; Resources - S.Y., N.D., A.İ., E.G.; Materials - S.Y., N.D., A.İ., E.G.; Data Collection and/or Processing - S.Y., N.D., A.İ., E.G.; Analysis and/or Interpretation - S.U., S.Y., N.D., E.Ç.Ş., D.E.; Literature Search - S.U., S.Y., N.D., E.G., A.İ.; Writing Manuscript - S.U., S.Y., N.D., O.B., E.Ç.Ş., D.E.; Critical Review - S.U., O.B., E.Ç.Ş., D.E., N.D., S.Y.

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