

Evaluation of the impact of warfarin time in therapeutic range on outcomes of patients with atrial fibrillation in Turkey: Perspectives from the observational, prospective WATER Registry

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Abstract

Background: Warfarin is highly efficacious in reducing stroke risk in patients with atrial fibrillation (AF). However, its safety and efficacy in stroke prevention is markedly influenced by its time in therapeutic range (TTR). The quality of anticoagulant therapy varies considerably among countries. Representative data concerning the quality of anticoagulant therapy and its effects on clinical outcomes in Turkey are lacking.

Methods: Warfarin in Therapeutic Range (WATER) registry is a prospective, observational study which followed 572 AF patients (mean age 67.3 ± 12 years; females 60%; 71% non-valvular AF) treated with warfarin.

Results: At a median of 22-month follow-up, the mean TTR value was 42.3 ± 18% (median: 40%) for the whole population and lower in non-valvular AF sub group than valvular AF subgroup (40.3 ± 18 vs. 46.9 ± 19, respectively, $p < 0.001$). Death, cardiac hospitalization and minor bleeding rates were higher in the group with TTR value < 40% than the group with > 40% (3.4% vs. 5.9%; 28.6% vs. 35.4%; 36.5% vs. 41.7%, respectively, all of them $p < 0.001$). A correlation analysis showed a negative correlation between age and TTR value ($r = -0.178$, $p < 0.001$). Mean CHA₂DS₂VASc score was 3.63 ± 1.5 and mean HASBLED score was 2.38 ± 1.01 in the non-valvular AF group. A negative correlation was observed between TTR levels and CHA₂DS₂VASc score.

Conclusions: WATER provides insight into the anticoagulation control status of AF patients in Turkey. The quality of anticoagulation was poor. Strategies should be undertaken by clinicians and patients to improve TTR. New oral anticoagulant agents may be perfect alternatives for non-valvular AF patients. (Cardiol J 2015; 22, 5: 567–575)

Key words: atrial fibrillation, warfarin, international normalized ratio, registry

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Introduction

Atrial fibrillation (AF) is a common cardiac arrhythmia that is predominantly non-valvular (NVAF) and its prevalence is likely to markedly increase in next several decades [1]. AF is a common cause of stroke, heart failure, hospitalization, and death in affected patients. AF patients have a 5-fold increase in the risk of stroke compared to individuals of the same age who are in sinus rhythm [1, 2]. For decades, warfarin has been the most widely utilized anticoagulant for stroke prophylaxis among AF patients. Warfarin is highly efficacious in reducing stroke risk, with a meta-analysis of several clinical trials reporting a 64% decrease in stroke risk among NVAF patients treated with warfarin [2, 3]. The major impediment to warfarin usage is the unpredictability of the level of anticoagulation in a given dose. Efficacy and safety of warfarin is markedly influenced by its time in therapeutic range (TTR), referring to the time patients treated with warfarin spend having an international normalized prothrombin time ratio (INR) within the therapeutic range, which requires regular blood test monitoring [4, 5]. A high TTR ($\geq 70\%$) is required for warfarin therapy to achieve a maximal effect. This reduces the risk of not only stroke and systemic embolism, but also bleeding [3–6]. Results from randomized clinical trials demonstrate that optimal TTR threshold is reached in approximately 60% of cases [7]. However, several observational studies and registries conducted on AF populations reported that AF patients spend only approximately half the TTR of warfarin [5, 8]. Lower TTR values in real life patients rather than randomized controlled trial patients have been confirmed consistently throughout different countries [8, 9]. Data on AF epidemiology and management in Turkey are quite limited and prospective mild- to long-term studies are lacking. In view of this fact, we undertook the registry of Warfarin in Therapeutic Range (WATER), a prospective observational study of AF in Turkey that enrolled consecutive AF patients who received warfarin. The purposes of this registry are to observe epidemiological and clinical characteristics of the AF population and to demonstrate the quality of anticoagulant therapy with warfarin and its effects on clinical outcomes.

Methods

Study design and study population

The WATER registry was designed as a multicenter, prospective, observational study with

a baseline visit at the time of patient enrolment. Between September 2011 and January 2014 we enrolled AF patients undergoing warfarin therapy for ≥ 6 months, who had been followed up and visited at an outpatient clinic by each institution. Patients were included if they were at least 18 years old and gave written informed consent for participation in the registry. The exclusion criteria were restricted to achieve a cohort close to real life. Furthermore, consecutive patients were included at each site in order to reduce selection bias. Only patients who did not give their informed consent and who did not comply with continuous warfarin therapy were excluded. Continuous warfarin therapy was defined as warfarin use without gaps exceeding 2 months. The warfarin dose during the follow-up was adjusted to the therapeutic range proposed by the 2010 European Society of Cardiology (ESC) guidelines for the management of AF. All data were captured through an electronic case report form (eCRF). The first 7 days after treatment had started or restarted, time after permanent discontinuation of warfarin and time > 5 days from temporary discontinuation were not included in the calculation of TTR. Periprocedural (anticoagulation bridging) INR and/or daily INR values during hospitalization were also excluded. Patients on home-monitoring or home-management were not included in the registry. Follow-ups were performed by the attending cardiologist with an office interview during INR control visits to assess the occurrence of clinical outcomes and events, as well as patients' compliance with warfarin therapy. The registry was performed according to the ethical principles of medical research involving human subjects, as specified in the Declaration of Helsinki.

Definitions

Event and status definitions were clearly defined on the eCRFs in order to achieve consistency among participating centers. TTR definition was described above. The estimation of TTR was based on the INR ranges that have been defined for individual patient's needs and clinical rationales (i.e. INR 2–3 for NVAF patients, INR 2.5–3.5 for valvular AF [VAF] patients with mitral prosthetic valve). Stroke was defined as a sudden onset of a focal neurologic deficit in a location consistent with the territory of a major cerebral artery. An event matching this definition but lasting less than 24 h was considered a transient ischemic attack. Intracranial hemorrhage consisted of hemorrhagic stroke and subdural or subarachnoid hemorrhage. Systemic embolism was defined as abrupt vascular

Table 1. Demographic and clinical characteristics of the study population.

	All patients (n = 572)	VAF (n = 169; 29.5%)	NVAF (n = 403; 70.5%)	P
Age [years]	67.28 ± 12.4	61.44 ± 13	69.91 ± 10	< 0.001
Sex (female)	343 (60%)	116 (69%)	227 (56%)	0.0067
Body mass index [kg/m ²]	27.77 ± 5.2	27.33 ± 4	27.96 ± 6	0.13
Paroxysmal AF	183 (32%)	24 (14%)	159 (39%)	< 0.001
CHA ₂ DS ₂ VASc score	–	–	3.64 ± 1.53	–
HASBLED score	–	–	2.38 ± 1	–
Creatinine clearance [mL/min]	72.49 ± 51.3	79.76 ± 33	66.88 ± 26	< 0.001
Heart failure	202 (35.3%)	55 (33%)	147 (36%)	0.39
Hypertension	328 (57.3%)	71 (42%)	257 (64%)	< 0.001
Diabetes mellitus	129 (22.5%)	23 (14%)	106 (26%)	< 0.001
Coronary artery disease	160 (28%)	21 (12%)	139 (34%)	< 0.001
Peripheral artery disease	50 (8.7%)	5 (3%)	45 (11%)	< 0.001
MI history	68 (11.8%)	7 (4%)	61 (15%)	< 0.001
CABG	55 (9.6%)	12 (7%)	43 (11%)	0.215
PCI	32 (5.5%)	2 (1%)	30 (7%)	0.0022
Stroke history	63 (11%)	14 (8%)	49 (12%)	0.19
Antiplatelet use	84 (14.7%)	23 (14%)	61 (15%)	0.364

VAF — valvular atrial fibrillation; NVAF — non-valvular atrial fibrillation; AF — atrial fibrillation; CABG — coronary artery bypass grafting; PCI — percutaneous coronary intervention

insufficiency associated with clinical or radiological evidence of arterial occlusion in the absence of another likely mechanism. Major bleeding was defined as a reduction in the hemoglobin level of at least 2 g/dL, a transfusion of at least 2 units of blood, or symptomatic bleeding in a critical area or organ. All other bleeding was considered minor. Duration of AF less than 7 days (with spontaneous return to sinus rhythm) or duration more than 7 days distinguished paroxysmal from persistent AF. Hypertension was defined as blood pressure above 140/90 mm Hg, diabetes as fasting blood glucose above 125 mg/dL, or the use of antihypertensive or antidiabetic drug therapy, respectively.

Statistical analysis

All variables collected in the eCRFs at baseline and all derived parameters were used in the statistical analysis. Binary, categorical, and ordinal parameters were summarized by means of absolute and percentage numbers within the various categories. Numerical data were summarized by means of standard statistics (i.e. mean, standard deviation, median, upper and lower quartile). Normally distributed continuous variables were expressed as mean (± standard deviation) and compared with unpaired Student's t-test. Skewed variables

were expressed as median (25–75 quartiles) and compared with the rank-sum test. Normality was assessed by the Shapiro-Wilk test. Differences between cohorts were tested for statistical significance using the χ^2 test for categorical variables. Among-group comparisons were made using a non-parametric test (Kruskal-Wallis test). Correlation analyses were carried out using parametric Pearson product-moment and nonparametric Spearman's rank correlation test. A 2-sided p-value of < 0.05 was considered statistically significant. The statistical analysis was performed using SAS v. 9.2.

Results

Patient characteristics

Between September 2011 and January 2014, of 986 patients screened, 572 (age 67.28 ± 12.4 years, 59.96% female) met eligibility criteria and agreed to participate. Seventy percent of the study population had NVAF and 32% of the patients had paroxysmal AF. Clinical and demographic characteristics of the study population, NVAF and VAF subgroups are shown in Table 1. The characteristics of the NVAF subgroup demonstrated older and sicker (accumulated comorbidities such as hypertension, diabetes, coronary artery disease,

Table 2. Clinical events during follow-up.

	All patients (n = 572)	Valvular atrial fibrillation (n = 169; 29.5%)	Non-valvular atrial fibrillation (n = 403; 70.5%)	P
Follow-up duration (months-median)	24.21 ± 14 (22)	25.8 ± 16 (21)	23.5 ± 13 (22)	0.096
TTR [%] (median)	42.26 ± 18.4 (40)	46.89 ± 18.9	40.32 ± 17.8	< 0.001
Death	26 (4.55%)	6 (3.5%)	20 (5%)	0.52
Stroke/TIA	31 (5.4%)	7 (4%)	24 (6%)	0.43
Intracranial bleeding	2 (0.35%)	0 (0%)	2 (0.5%)	1
Major bleeding	29 (5.1%)	6 (3.5%)	23 (5.7%)	0.4
Minor bleeding	222 (38.8%)	64 (38%)	158 (39%)	0.78
Cardiac hospitalization	181 (31.6%)	53 (31%)	128 (32%)	1

Valvular atrial fibrillation; Non-valvular atrial fibrillation; TTR — time in therapeutic range; TIA — transient ischemic attack

Table 3. Clinical events according to median time in therapeutic range (TTR) level.

	TTR ≥ 40% (n = 318; 56%)	TTR < 40% (n = 254; 44%)	P
Death	11 (3.5%)	15 (5.9%)	0.0003
Stroke/TIA	18 (5.7%)	13 (5.1%)	0.14
Intracranial bleeding	2 (0.6%)	0 (0%)	1
Major bleeding	18 (5.7%)	11 (4.3%)	0.085
Minor bleeding	116 (36.5%)	106 (41.7%)	< 0.0001
Cardiac hospitalization	91 (28.6%)	90 (35.4%)	< 0.0001

TIA — transient ischemic attack

reduced renal function etc.) patients than the Valvular atrial fibrillation subgroup.

Quality of warfarin treatment and outcomes

TTR was calculated for all patients and separately for subgroups. The mean follow-up time was 46.9 ± 19 (median 22) months. During the follow-up period, the mean TTR for all patients on the WATER registry was 42.26% (median 40%). TTR value of Non-valvular atrial fibrillation and Valvular atrial fibrillation subgroups was 40.3% and 46.9%, respectively (p < 0.001). In terms of outcome events, there was no significant difference between the subgroups (Table 2). The study population was divided into two groups according to the median TTR level. Outcome event ratios of these groups are presented in Table 3. The TTR value ≥ 40% group had lower death, minor bleeding and cardiac hospitalization ratios than the TTR value < 40% group. A correlation analysis showed a negative correlation between TTR value and age in the whole study population (r = -0.178, p < 0.001) (Fig. 1).

CHA₂DS₂VASc score and outcomes

Stroke risk was high in the Non-valvular atrial fibrillation subgroup (mean CHA₂DS₂-VASc score of 3.6 ± 1.5). The Non-valvular atrial fibrillation group was dissected according to

CHA₂DS₂VASc score and TTR values of these groups are presented in Figure 2. The median value of CHA₂DS₂VASc score was 4 in Non-valvular atrial fibrillation patients. The CHA₂DS₂VASc < 4 group had lower death, minor bleeding and cardiac hospitalization rates than the CHA₂DS₂VASc ≥ 4 group. They also had lower stroke and major bleeding rates than the CHA₂DS₂VASc ≥ 4 group but the differences were not statistically significant (Table 4). TTR value of CHA₂DS₂VASc ≥ 4 group was lower than the one of CHA₂DS₂VASc < 4 group and there was a negative correlation between the CHA₂DS₂VASc score and TTR value (r = -0.155, p = 0.018).

HASBLED score and bleeding events

The mean HASBLED score of the Non-valvular atrial fibrillation population was 2.38 ± 1 (median 3). Major bleeding events were observed in 23 cases in the Non-valvular atrial fibrillation group. They had a higher HASBLED score than the patients without major bleeding, however the difference was not statistically significant (2.73 ± 1 vs. 2.36 ± 1, p = 0.09). Minor bleeding events were observed in 158 cases in the Non-valvular atrial fibrillation group and they had a significantly higher HASBLED score than the cases without minor bleeding events (2.77 ± 0.9 vs. 2.12 ± 1, p < 0.0001).

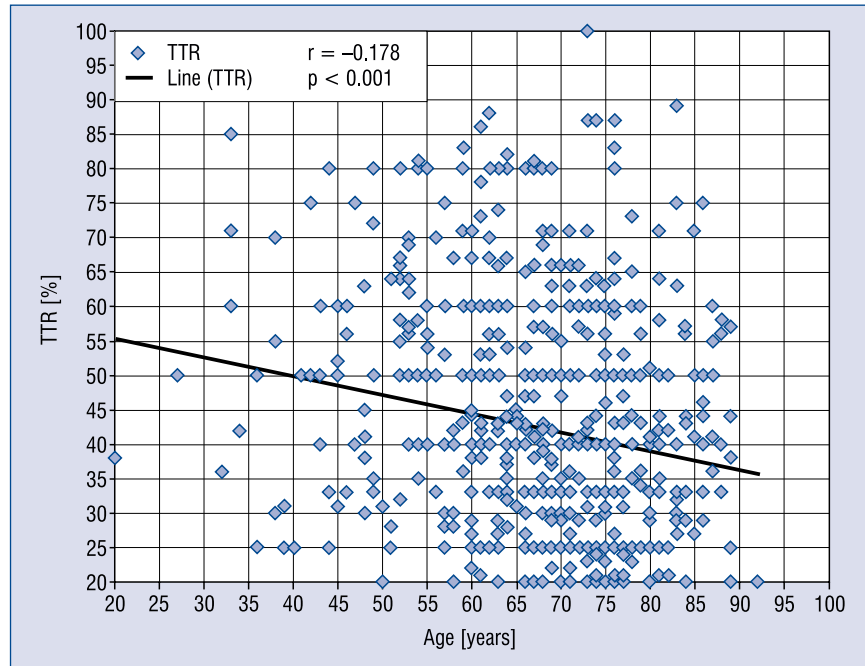


Figure 1. Correlation between age and time in therapeutic range (TTR) level.

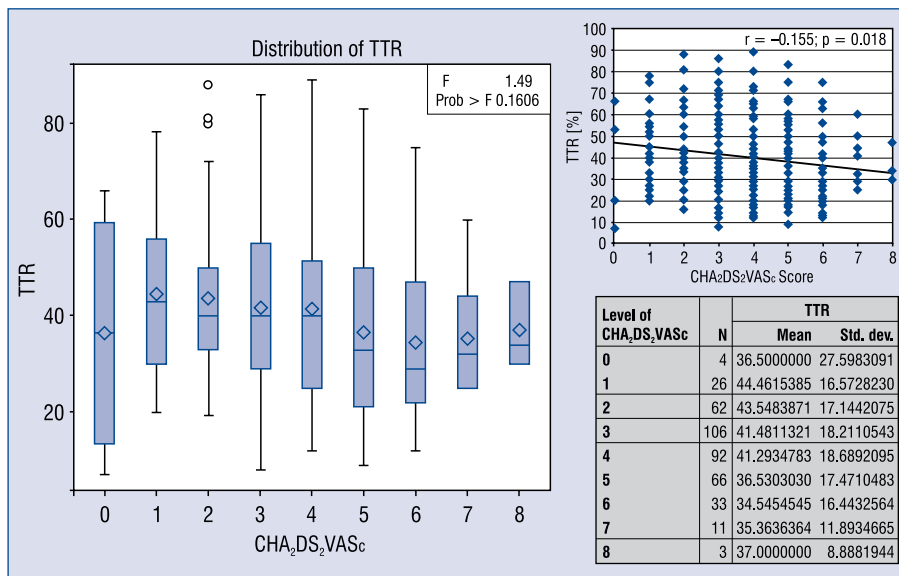


Figure 2. Distribution of time in therapeutic range (TTR) levels according to CHA₂DS₂VAS_c score.

Discussion

AF is the most common chronic rhythm disorder. It is present in over 4 million patients in Europe with a prevalence of 5–15% in patients over 80 years of age [1, 10]. Since AF carries certain morbidity, with ischemic stroke and other embolisms, during the last decade particular atten-

tion has been paid to the management of patients with AF. Several guidelines have been issued and proper anticoagulation treatment has been recommended [2, 11, 12]. However, a large percentage of AF patients receive suboptimal care. Few studies have been conducted with similar prevalence and incidence ratios in the Turkish population [13, 14]. Notwithstanding this fact, a cohort study pointed

Table 4. Baseline renal function, time in therapeutic range levels and clinical events according to median CHA₂DS₂VASc score.

CHA ₂ DS ₂ VASc score	≥ 4 (n = 205)	< 4 (n = 198)	P
Creatinine clearance [mL/dk]	57.2 ± 24.3	76.9 ± 24.3	< 0.001
TTR value [%]	38.3 ± 17.6	42.4 ± 17.8	0.019
Death	19 (9%)	1 (0.5%)	< 0.001
Stroke/TIA	16 (8%)	8 (4%)	0.14
Intracranial bleeding	1	1	1
Major bleeding	16 (7.8%)	7 (3.5%)	0.085
Minor bleeding	116 (57%)	42 (21%)	< 0.001
Cardiac hospitalization	98 (48%)	30 (15%)	< 0.001

TTR — time in therapeutic range; TIA — transient ischemic attack

out that only 42% of eligible patients received oral anticoagulants [13]. Warfarin is a common anticoagulation strategy in Turkish patients with AF. However, there are no prospective, real life data about quality of anticoagulation control, factors which influence TTR values, the relationship between TTR value and clinical outcomes.

Registries are very important as means of identifying possible gaps between recommended therapies and actual everyday practice. National registries are always needed, since each country has specific features and data from other countries that may not apply elsewhere.

This registry aims to answer these questions in the Turkish population and exhibits unique results. The demographic profile of the registry population showed that nearly 70% of the AF population had non-valvular etiology. NVAF patients represented an older and sicker population than VAF population. These demographic characteristics are compatible with the European and American registries except for a higher percentage of the VAF group in the whole AF population [10, 15, 16]. These findings are unsurprising and compatible with a higher prevalence of acute rheumatic fever and rheumatic valve disease in Turkey, and also clearly exhibited that rheumatic heart disease and its late complications are still a public health concern in our country. Female dominance was more evident in the VAF group than the NVAF group and NVAF patients had paroxysmal AF more often but had persistent and permanent AF less often than VAF patients. These demographic and clinical characteristics were previously validated in the EURObservational Research Program on Atrial Fibrillation Pilot survey [1].

AF patients have a 5-fold increase in the risk of stroke and a 2-fold increase in the risk of mortality

compared to individuals of the same age who are in sinus rhythm [2, 17]. The registry results show that AF patients have a 5-fold increase in stroke risk and a 4-fold increase in mortality compared to the general Turkish population [18–20]. The WATER registry showed that 1 in 3 patients was hospitalized due to cardiac causes and 4 in 10 patients had a minor bleeding event at their 2-year follow-up. These results reflected the health burden of AF in the Turkish population. However, these results should be evaluated cautiously according to the selection bias of the registry. Although a consecutive enrolment and selection of ‘representative sites’ (outpatients and inpatients) was used to provide a real life data set, the WATER registry only enrolled AF patients undergoing warfarin therapy. Recent data have demonstrated that while 87% of the AF patients were high risk patients, only 42% of these patients were on oral anticoagulant treatment in Turkey [13]. In this context, higher stroke and mortality rates should not be a surprise in the real life setting of Turkey.

Warfarin is still the main anticoagulation strategy for stroke prevention in Turkey but optimal use of warfarin in clinical practice is challenged by its narrow therapeutic window. Anticoagulation quality assessed by TTR has been closely associated with adverse outcomes, i.e., stroke, hemorrhage and mortality. In this registry, TTR levels were calculated on the basis of the INR ranges that have been defined for individual characteristics rather than simply assuming that the target range is 2.0–3.0. Although the VAF group had higher TTR values than NVAF, the registry demonstrated much poorer anticoagulation control in real life settings than similar European registries [10, 16]. As a result, patients were spending most of their time outside of the recommended therapeutic range. The effects

of TTR on clinical outcomes were also confirmed in the registry.

Albeit a very low mean TTR level, the study population was divided into two groups according to median TTR of 40%. The lower TTR group had higher death, minor bleeding, and cardiac hospitalization rates. Although major bleeding and stroke rates were similar between the two groups, lower event rates may have had a role in these results. The quality of anticoagulation was poorer in the older population and a negative correlation was evident between age and TTR level. These results have conflicted with previous similar registries. Witt et al. [21] identified that the older age group (age > 70) independently predicted INR stability. Similar results have been submitted by the VARIA Study which asserted that the group age > 55 had a predicted lower TTR [22]. However, both studies issued quality of anticoagulation control in patients who received oral anticoagulation for any indication (AF, venous thromboembolism, prosthetic valve etc.). Additionally, many previous studies which focused on AF population found old age to be associated with lower TTR [23, 24]. Possible explanations of the negative correlation between age and TTR are age related changes in drug metabolism, higher prevalence of co-morbidities in older patients, decline in cognitive function with increasing age and possible under treatment of the elderly with lower INR goals. Relationships between the older age, decreased renal function and lower TTR were also confirmed by the NVAf subgroup of WATER Registry. As an older group, NVAf patients may have lower cognitive function than the VAF group. We know that cognitive function has a main role in compliance of drug and INR visits. However, because the patients in the WATER Registry attended cardiology clinics regularly and received specialized care, we believe that lower TTR was not a consequence of a lack of strict INR control or undertreatment of older patients with lower INR targets and patients' access to healthcare.

Given the higher prevalence of co-morbidities in patients with NVAf, their potential association with lower TTR is of note. Anticoagulation control may be more challenging for patients with these co-morbidities. Nelson et al. [23] showed that heart failure, diabetes and previous strokes were associated with the greatest likelihood of lower TTR. WATER results also confirmed the effects of renal function on anticoagulation control. The group whose mean TTR value was lower than the median level had lower creatinine clearance than the group

whose mean TTR value was higher than the median level (67.4 ± 27 vs. 73.3 ± 30 mL/min respectively, $p < 0.001$). Furthermore, there was a significant positive correlation between the creatinine clearance and TTR value ($r = 0.137$, $p = 0.001$). We know that heart failure, chronic kidney disease and diabetes affect the drug pharmacokinetics and finally pharmacodynamics. An additional explanatory mechanism is a possible interaction between warfarin and multiple drugs administered to these patients. These co-morbidities may also decline cognitive function, which affects drug compliance.

If good anticoagulation control cannot be achieved within the usual care setting, specialized anticoagulation management such as anticoagulation clinics or handheld patient INR meters are validated alternative options [5, 25]. Finally, substitution with newer oral anticoagulants is inevitable in patients with NVAf.

WATER results also proved that patients with a higher CHA₂DS₂VASc score were more likely to have a lower TTR level in the NVAf subgroup. We may hypothesize that factors contributing to the score have a major impact on drug metabolism, cognitive function and finally INR stability. Although the score does not incorporate renal function, incorporated co-morbidities such as age, hypertension, diabetes, and vascular disease could be associated with concomitant chronic kidney disease, which is known to reduce anticoagulation stability. [5, 22–24]. The registry results confirmed the deterministic and prognostic role of CHA₂DS₂VASc score. Lower death, minor bleeding and cardiac hospitalization rates were observed in the group whose CHA₂DS₂VASc score, was higher than the median value. However there were no statistically significant differences between these groups in terms of major bleeding and stroke rates. Lower event rates, particularly major bleeding rates, may help assess the objectivity of these results. Additional dissecting the groups for higher than median value of CHA₂DS₂VASc score may result in the inadvertent, incorrect classification of many patients who had a higher risk of stroke as lower risk patients.

The value of the HASBLED score was also confirmed with the higher score of patients who had a minor bleeding event during the follow-up. Similarly with CHA₂DS₂VASc score, patients who had major bleeding had a statistically insignificant trend for higher HASBLED scores. As mentioned above, lower event rates may preclude reaching statistically significant differences.

Limitations of the study

The study findings should be interpreted in the light of some limitations. Main limitations include the observational design; relatively small sample size, lower outcome rates (i.e. major bleeding, intracranial bleeding etc.) and limited 2-year follow-up. Because the registry included only 3 centers from the same city, results may not be reflective of the whole country and should not be generalized. As such, we cannot claim that our findings are clearly representative of warfarin management in other centers. Certainly a larger study conducted in more centers over different geographical regions would be desirable. Moreover, some of the data were self-reported and therefore might not have been accurate. We could not assess scheduled interruptions of oral anticoagulants (i.e. periprocedural bridging), which may have resulted in the underestimation of the TTR levels. Finally, because TTR values do not capture the full amplitude of INR fluctuations (either outside or within the therapeutic window), the TTR is a relatively crude measure of anticoagulation control. Lind et al. [26] showed that standard deviation of transformed INR is a better predictor of mortality, stroke, bleeding and hospitalization than the TTR in patients with AF receiving warfarin therapy. This approach may explain the difference of event ratios between the patients who had similar demographic profiles and TTR levels in WATER population.

Conclusions

In conclusion, the quality of anticoagulation with warfarin in daily clinical practice in Turkey is poor. This could have serious implications, as it is expected to adversely affect patient outcomes. These findings have implications for health policy. Strategies should be undertaken by the clinicians to improve TTR. Educational programs directed at patients are urgently needed to improve the quality of anticoagulation in Turkey. Frequent, even weekly, dose adjustments for the majority of INRs out of range is a simple concept that is associated with improved TTR and clinical outcome [27]. Systems that implement algorithm based dosing for AF patients on warfarin or widespread use of point of care testing devices for the measurement of INR may improve the management of patients [27–29]. If good anticoagulation control cannot be achieved with warfarin, new oral anticoagulants are inevitable strategies in patients with NVAf. Nevertheless, regarding the higher prevalence of valvular AF in Turkey than Europe and the United

States, strategies should not be overlooked to improve TTR in these patients.

Conflict of interest: None declared

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