The awareness, efficacy, safety, and time in therapeutic range of warfarin in the Turkish population: WARFARIN-TR

*Ahmet Çelik, Servet İzci[1], Mehmet Ali Kobat[2], Ahmet Hakan Ateş[3], Abdülkadir Çakmak[4], Yasin Çakıllı[5], Mehmet Birhan Yılmaz[6], Mehdi Zoghi[7], on behalf of WARFARIN-TR Study Collaborates**

Department of Cardiology, Faculty of Medicine, Mersin University; Mersin-*Turkey*, [1]Department of Cardiology, Koşuyolu Education and Research Hospital; İstanbul-*Turkey*, [2]Department of Cardiology, Faculty of Medicine, Fırat University; Elazığ-*Turkey*, [3]Department of Cardiology, Samsun Education and Research Hospital; Samsun-*Turkey*, [4]Department of Cardiology, Faculty of Medicine, Amasya University; Amasya-*Turkey*, [5]Department of Cardiology, Siyami Ersek Education and Research Hospital; İstanbul-*Turkey*, [6]Department of Cardiology, Faculty of Medicine, Cumhuriyet University; Sivas-*Turkey*, [7]Department of Cardiology, Faculty of Medicine, Ege University; İzmir-*Turkey*

Abstract

Objective: The awareness, time in therapeutic range (TTR), and safety of warfarin therapy were investigated in the adult Turkish population.

Methods: This multicenter prospective study includes 4987 patients using warfarin and involved regular international normalized ratio (INR) monitoring between January 1, 2014 and December 31, 2014. TTR was calculated according to F.R. Roosendaal's algorithm. Awareness was evaluated based on the patients' knowledge of warfarin's affect and food–drug interactions.

Results: The mean TTR of patients was 49.52±22.93%. The patients with hypertension (55.3%), coronary artery disease (23.2%), congestive heart failure (24.5%), or smoking habit (20.8%) had significantly lower TTR levels than the others. Of the total number of patients, 42.6% had a mechanical valve, 38.4% had non-valvular atrial fibrillation (AF), and 19% had other indications for warfarin. Patients with other indications had lower TTR levels than those with mechanical valve and non-valvular AF (p=0.018). Warfarin awareness decreased in higher age groups. The knowledge of warfarin's food–drug interactions was 55%. People with higher warfarin awareness had higher TTR levels. Patients with ≤8 INR monitoring/year had lower TTR levels (46.4±25.3 vs. 51.1±21.3, respectively, p<0.001) and lower awareness (44.6% vs. 60.6%, p<0.001) than patients with ≥8 INR monitoring/year. In this study, 20.1% of the patients had a bleeding event (major bleeding 15.8%, minor bleeding 84.2%) within a year.

Conclusion: Both the mean TTR ratios and awareness of the Turkish population on warfarin therapy were found to be low. It was thought that low TTR levels of the Turkish population may be caused by the low awareness of warfarin, warfarin's food–drug interactions, and high rates of concomitant diseases. *(Anatol J Cardiol 2016; 16: 595-600)*

Keywords: time in therapeutic range; warfarin; Turkish population

Introduction

Warfarin is a drug that inhibits the synthesis of clotting factors II, VII, IX, and X and protein C and S (1). The anticoagulant activity of warfarin depends on the clearance of functional clotting factors from the systemic circulation. The efficacy and safety of warfarin are strongly dependent on the intensity of anticoagulation measured as the international normalized ratio (INR). The initiation and management of warfarin therapy is often difficult because it has a narrow therapeutic range, drug and food interactions, and need for continuous patient education and routine INR monitoring (2). Increased time in the therapeutic range (TTR) is associated with a lower risk of thromboembolic events and bleeding in patients using warfarin (3). All physicians aim to provide higher TTR levels for their patients. Although patients may use the same dosage, never change their diets, and never use any different drug, they could not sometimes obtain the target INR. Differences in TTR values have been observed in various countries because of patient characteristics or country socioeconomic and healthcare standards (4–6).

This study examined TTR levels, bleeding ratios, warfarin dosage, and the reason for warfarin usage, concomitant diseases, and patient awareness of warfarin in all regions of Turkey.

Methods

This multicenter prospective study included 42 centers from 24 cities in 7 regions of Turkey. Patients (n=4987) attended follow-ups for 12 months. The sample size calculations were analyzed by

Address for correspondence: Dr. Ahmet Çelik, Mersin Üniversitesi Tıp Fakültesi, Kardiyoloji Anabilim Dalı, Mersin-*Türkiye*
Phone: +90 531 792 79 10 Fax: +90 324 241 00 05 E-mail: ahmetcelik39@hotmail.com
Accepted Date: 10.09.2015 **Available Online Date:** 19.11.2015

DOI:10.5152/AnatolJCardiol.2015.6474

Power analysis according to the density of the regional population (Table 1) and according to the Turkey Statistical Institute data. The data, including key patient characteristics, treatment, concurrent illnesses, and bleeding complications, were recorded. The study protocol was approved by the local Ethics Committee. The patients' data were obtained and recorded during routine clinic follow-up, and the INR values were recorded from the Hospital records.

Patients regularly using warfarin for any reason and attending routine INR monitoring were consecutively included in the study. Patients who were under 18 years, had an inconsistent use of warfarin, or did not visit INR monitoring sessions consistently were excluded from the study (Table 1). The patients' INR data were extracted for the period of January 1, 2014–December 31, 2014. In the event of patients with more than one indication of anticoagulation treatment with warfarin, the main reason was listed as the warfarin indication. TTR was calculated according to F.R. Roosendaal's algorithm with linear interpolation (7). Patients' INR values were recorded between each measured INR as daily. Patients with time between any two measurements of ≥59 days (4.8% of the intervals between two INR measurements) were excluded from the TTR calculation and the study. TTR was calculated as the proportion of days with INR values between the target INR (2.0–3.0 or 2.5–3.5). The target of INR was 2.5 (range 2.0–3.0) in patients with a mechanical aortic valve, non-valvular AF, and other reasons. The target of INR value was 3 (2.5–3.5) in patients with a mechanical mitral valve and/or mechanical heart valves in both the aortic and mitral position (8). We recorded the patients' mean warfarin dosages as ≤2.5 mg, 2.5–5 mg, 5–10 mg, or ≥10 mg daily. The patients' awareness of warfarin's affect and food–drug interactions were determined by a simple questionnaire according to their answers (Yes/No). We asked the patients the following questions: Do you know the reason of your warfarin usage? and Do you know anything about the food–drug interaction of warfarin? Individual characteristics were used to assess the risk of awareness of warfarin therapy. The included individual level factors were respondent's age (18–35, 36–50, 51–65, 65–80, ≥81 years) and gender (male, female). Major bleeding was defined as a reduction in the hemoglobin level of at least 2 g/L, transfusion of at least 2 units of blood, or symptomatic bleeding in a critical area or organ. All other bleeding was accepted as minor bleeding.

Statistical analysis

In this study, the continuous variables were presented as mean±standard deviation (mean±SD), and the categorical variables were expressed as number and percentage (%). The continuous variables were compared across the groups using independent samples t-test or Mann–Whitney U test. The categorical variables were compared using the chi-square test. Two proportions z test was used when we obtained differences in more than two categories with the chi-square test. Comparisons between more than two groups were performed using one-way analysis of variance (ANOVA) and Tukey posthoc test. The bleeding types and ratios were analyzed according to the antiaggregant use with chi-square test.

Table 1. The population density of regions in WARFARIN-TR study

Regions	Population density of provincial and district centers	Weighted number of patients	%
Black Sea	8.500.000	625	12.8
Marmara	17.400.000	1280	13.1
Agean	8.900.000	655	17.1
Mediterranean Sea	8.700.000	640	9.0
South East Anatolian	6.600.000	485	12.5
East Anatolian	6.100.000	449	25.7
Central Anatolian	11.600.000	853	9.7
Total	67.800.000	4987	100.0

Data are presented as numbers of patients (percentage)

In the graphical representation of bar and pie charts were used. A p value less than 0.05 was considered statistically significant.

Results

The characteristics of 4987 patients (male: 44.9%) followed up for 9.6±2.2 months and the baseline characteristics of patients on warfarin therapy are summarized in Table 2. The mean time of warfarin usage was 47.8±45.8 months (min. 6 month–max. 276 months). The patients' mean percentage of TTR level was 49.52±22.93. Figure 1 shows the percentages of the TTR levels of patients. The rate of TTR was similar according to gender (49.2±22.8% in females and 49.9±22.9 in males, p=0.283). The patients with hypertension (48.54±22.70 vs. 50.72±23.16, p=0.001), coronary artery disease (47.72±22.99 vs. 50.05±22.89, p=0.002), congestive heart failure (48.05±23.23 vs. 49.99±22.81, p=0.010), and smoke (48.26±22.67

Table 2. The baseline characteristics of WARFARIN-TR study patients

Descriptive	
Age, years	60.7±13.5
Hypertension, %	55.3
Diabetes mellitus, %	20.9
Smoke, %	20.8
Hyperlipidemia, %	21.4
Congestive heart failure, %	24.5
Coronary artery disease, %	23.2
Chronic renal failure, %	6.1
End-stage renal disease, %	2.1
Cerebrovascular disease, %	9.3
Pulmonary embolism, %	5.0
Deep venous thrombosis, %	5.5
Time of warfarin usage, month	47.8±45.8
Number of INR monitoring within a year	10.2±3.4

Data are presented as the mean values±SD or numbers of patients (percentage), as appropriate

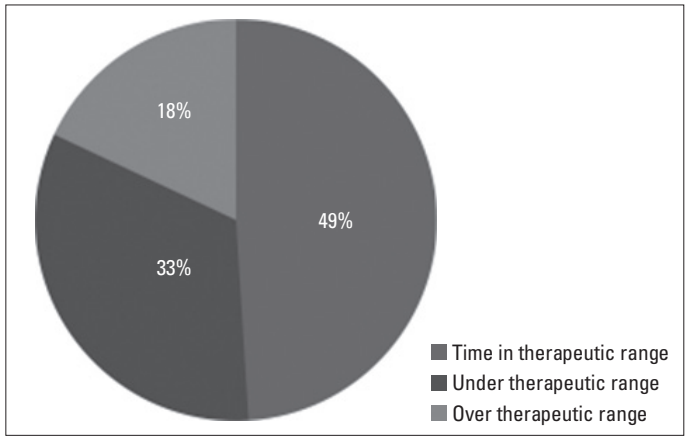


Figure 1. The evaluation of time in therapeutic range in patients who are on warfarin therapy

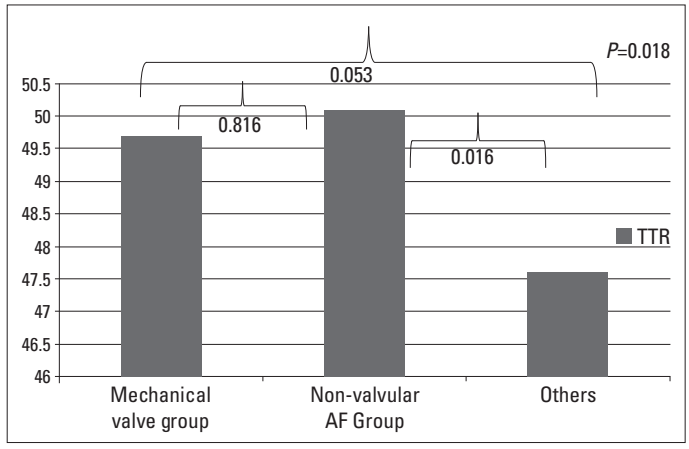


Figure 2. The analysis of TTR levels of patients according to their warfarin indication

vs. 49.84±22.99, p=0.049) had lower TTR levels than others. The patients with chronic kidney disease had higher TTR levels than others (53.5±21.6 vs. 49.2±22.9, p=0.001). Of the total number of patients, 2124 (42.6%) had a mechanical valve, 1918 (38.4%) had non-valvular AF, and 985 (19%) had other conditions as warfarin indications, including chronic pulmonary embolism, ischemic stroke, deep venous thrombosis, thrombus in any heart chamber, peripheral arterial thrombosis, and rheumatic mitral stenosis with AF. TTR levels according to warfarin indication were 50.1±22.9 in non-valvular AF patients, 49.7±22.9 in mechanical valve patients, and 47.7±22.8 in patients with other warfarin indications (p=0.018; Fig. 2). Based on dosage, 9.2% of patients used ≤2.5 mg/daily of warfarin, 55.7% used 2.5–5 mg/daily, 32.4% used 5–10 mg/daily, and 2.7% used ≥10 mg/daily. The rate of awareness of the Turkish population was low (the knowledge of warfarins' food–drug interaction was 55%) in Turkey. People who were aware of the food–drug interactions of warfarin had higher TTR levels (52.75±22.91 vs. 45.56±22.34, p<0.001). The median time of warfarin usage was significantly higher in patients who were aware of food–drug interactions than others [36 (6–276) vs. 26 (6–250), p<0.001]. There was no significant difference between gender and awareness of warfarin therapy in the Turkish population (55.4% of females had awareness and 54.4% of males had awareness, p=0.440). Figure 3 shows the awareness of warfarin therapy in Turkish patients according to their age groups. It was observed that decreasing age was associated with increased awareness. The awareness of patients according to the age groups were 72.3% in 18–35 years (n=249), 67.9% in 36–50 years (n=858), 58% in 51–65 years (n=1877), 45.8% in 65–80 years (n=1746), and 35% in ≥81 years (n=257) (p<0.001). The TTR levels were similar in different age groups (p=0.342). The patients were divided into two groups according to their INR count/year. The patients who obtained ≤8 INR monitoring a year (n=1752) had lower TTR levels than those who obtained >8 INR monitoring a year (n=3235) (46.49±25.38 vs. 51.15±21.31, respectively, p<0.001). The patients who obtained ≤8 INR monitoring a year had lower awareness than others (44.6% vs. 60.6%, p<0.001). The bleeding ratios and awareness of patients according to warfarin indications are shown in Figure 4. The bleeding ratios were different between mechanical valve and non-valvular AF groups (p=0.019), and the awareness ratios were different in both groups (p<0.001).

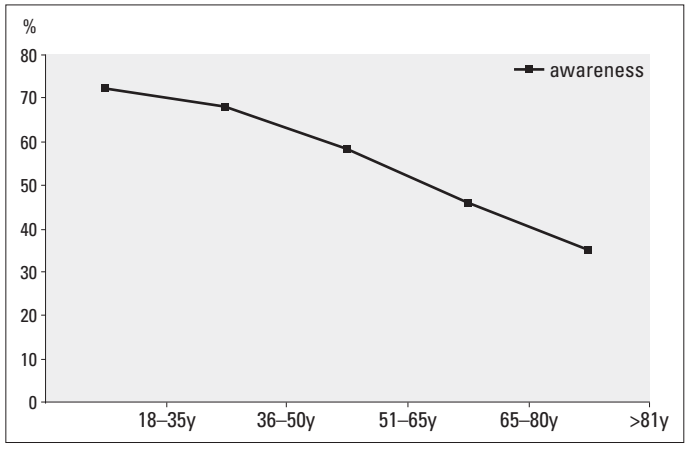


Figure 3. The awareness of patients according to the age groups (72.3% in 18–35 years, 67.9% in 36–50 years, 58% in 51–65 years, 45.8% in 65–80 years and 35% in ≥81 years, *P*<0.001)

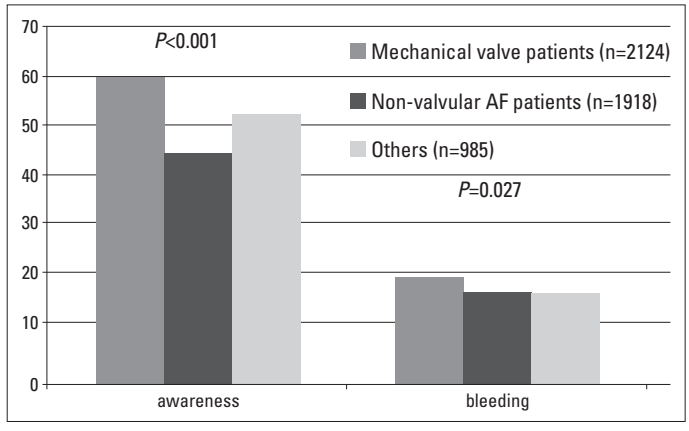


Figure 4. In One-Way ANOVA analysis; the awareness and bleeding ratios of the awareness and bleeding ratios of Turkish patients according to their warfarin indication (The awareness ratio of mechanical valve patients was 62.5%, non-valvular AF patients 46.9%, and others 55%. The bleeding ratio of mechanical valve patients was 21.5%, non-valvular AF patients 18.5%, and others 18.4%)

It was observed that 20.1% of all patients had a bleeding event [major bleeding 15.8% (3.2% of all patients), minor bleeding 84.2%] within a year (Table 3). In addition, 70.9% of INRs were over the therapeutic range, 24.6% of INRs were at the therapeutic range, and 4.6% of INRs were under the therapeutic range. There is no significant difference in the bleeding ratios of patients according to the knowledge about the reason of warfarin usage (21.9% in patients with the knowledge vs. 19.8% patients without the knowledge, p=0.171) and knowledge of food–drug interactions (20.3% in knowing patients vs. 19.3 in not knowing patients, p=0.203). Moreover, 24.2% of patients (1205) were using an antiaggregant with warfarin. Most of them (96.2%) were using acetylsalicylic acid (100 mg) as an antiaggregant agent. The bleeding ratios of patients who used an antiplatelet agent with warfarin had higher bleeding ratios (Table 4).

Table 3. The analysis of bleeding complications of patients within a year

Type of bleeding	n	%
Intracranial bleeding	58	5.8
Gastrointestinal bleeding	100	10.0
Gingival bleeding	191	19.0
Intra-articular bleeding	16	1.6
Nosebleed	264	26.3
Ecchymosis	238	23.7
Hematuria	120	11.9
Menorrhagia	18	1.8
Total	1005	100.0

Data are presented as numbers of patients (percentage)

Table 4. The bleeding ratios according to the concomitant antiplatelet agent usage

	Patients using warfarin+ antiplatelet agent (n=1205)	Patients using only warfarin (n=3782)	*P*
Any bleeding event n, (%)	336, (27.9%)	650, (17.2%)	<0.001
Major bleeding n, (%)	52, (4.3%)	106, (2.8%)	<0.001
Minor bleeding n, (%)	204, (25.1%)	363, (14.4%)	<0.001

A chi-square test was used for analysis of patients bleeding ratio according to the concomitant antiplatelet agent usage. Data are presented as numbers of patients (percentage). *P* was accepted <0.05 as significant.

Discussion

This study was the first to investigate such a large population of patients' awareness and TTR levels of warfarin therapy in Turkey. The TTR levels of patients in the Turkish population were low. Patients with concomitant disease, such as hypertension, coronary artery disease, congestive heart failure, or smoking habit, had significantly lower TTR levels than the others. The possible interactions of warfarin and drugs used in the treatment of these diseases and/or the diseases themselves may affect the TTR levels. The rate of these diseases was high in Turkish patients on warfarin, and thus, could be a reason for low TTR levels. The awareness of warfarin in the Turkish population did not seem adequate, and at older ages, the awareness of warfarin decreased. Therefore, age may be a leading factor affecting the awareness of warfarin in the Turkish population.

Vitamin K antagonists such as warfarin are used worldwide to reduce the risk of stroke, but the benefits are only seen in a narrow therapeutic range. The therapeutic range is defined as the range of concentrations at which a drug or any other therapeutic agent is effective with minimal toxicity to most patients. Treatment with warfarin needs regular laboratory-guided dose adjustments because response to treatment is affected by many factors, such as food–drug interactions (9). The lowest risk of stroke and bleeding is reached by maximizing TTR, with a target INR as a warfarin indication. However, large variations in TTR occur between individuals, sites, and countries, all of which affect patient outcomes (10).

The main reasons for warfarin usage in the Turkish population were mechanical valve (42.6%) and non-valvular AF (38.4%). Although the patients with mechanical valves had more awareness than the non-valvular AF patients, this situation did not reflect on the TTR rates. At the same time, the patients with mechanical valves had higher bleeding ratios. The higher target INR requirement in mechanical valve patients may be the reason for their higher bleeding ratio. Currently, warfarin is the only option for mechanical valve patients, but new oral anticoagulants have become available for patients with non-valvular AF, pulmonary embolism, deep venous thrombosis, ischemic stroke, left ventricular mural thrombus after acute myocardial infarction, and left ventricular assist devices (11–14).

The first epidemiologic registry about non-valvular AF was started in Turkey with the AFTER study (15). In the AFTER study, it was shown that the TTR level was detected in 41.3% of the patients with AF in Turkey (16). On the other hand, patients treated with warfarin were outside the INR target range 32.1% of the time in British population (3). However, these studies included only patients who had an inpatient diagnosis of non-valvular AF. In our study, we found that the Turkish population patients treated with warfarin had 49.5% TTR levels. Karacağlar et al. (17) analyzed the patients with AF in a single-center study, and they found that 167 of 202 patients had regular INR monitoring and the TTR levels were 83.5%. However, they had a very small sample size for reflecting Turkish data. In another study from Turkey, Ertaş et al. (18) showed that the TTR levels of 107 patients with AF in a single-center study were 47.1%. Recently, the ORBIT-AF study showed that the median TTR of AF patients in the US was 68% (19). Many factors such as socioeconomic status, race, and awareness of food–drug interactions of warfarin may affect our worst results. We thought that we must increase the TTR values of patients on warfarin therapy in Turkey at least by educating patients and physicians. Lindh et al. (20) showed that Swedish doctors

in the vast majority of cases refrain from prescribing NSAIDs to patients already on warfarin. There was no study showing the approach of Turkish physicians with respect to the patients on warfarin. In particular, Turkish physicians should be more aware of the interaction between NSAIDs and warfarin to reduce the bleeding complications and increase the TTR levels of patients. The drugs interacting with warfarin should be listed and then we need to raise the awareness of these drugs in Turkish physicians.

The awareness of warfarin therapy is extremely important to reduce the risk of stroke and bleeding. Because of its narrow therapeutic window, a slim line between bleeding and stroke risk is maintained with respect to warfarin patients. Even when the INRs are on target, sometimes stroke and bleeding complications can occur. In this study, 24.6% of the bleeding complications occurred at the therapeutic range, and 4.6% of them occurred below the therapeutic range. In this study, regular INR monitoring was associated with both high TTR levels and high awareness rates. Thus, if the awareness of warfarin, particularly its food–drug interactions, and the necessity of regular INR monitoring are increased, the complications of warfarin can be decreased.

Study limitations

The main limitation of the study was not evaluating the effect of other drugs on TTR that patients regularly use with warfarin, except antiaggregant agents. The other limitation is including and evaluating different warfarin indication groups in the same study.

Conclusion

The TTR levels of the Turkish population were low. Warfarin education for food–drug interactions and the necessity of regular INR monitoring should be performed in the Turkey Health System, particularly for older patients, to increase the TTR levels.

Appendix (*numbers indicate cities)

Collaborators: *Hüseyin Altuğ Çakmak[9], Abdülmecid Afsin[10], Ahmet İlker Tekkesin[6], Gönül Açıksarı[11], Mehmet Erdem Memetoğlu[12], Fatma Özpamuk Karadeniz[13], Ekrem Şahan[14], Mehmet Hayri Alıcı[15], Yüksel Dereli[16], Ümit Yaşar Sinan[17], Elif Çekirdekçi[18], Servet Altay[19], Deniz Elcik[20], Salih Kılıç[8], Nazlı Akciğer[21], Eyüp Özkan[22], Mine Durukan[23], Yusuf Aslantaş[24], Bahadır Şarlı[22], Çağrı Yayla[25], Murat Bilgin[26], Mehmet Kadri Akboğa[25], Tolga Han Efe[26], Ali Sabri Seyis[27], Zeynep Yapan Emren[28], Kamil Tülüce[29], Nurullah Çetin[29], Ali Kemal Kalkan[30], Fatih Aytemiz[31], Selcen Yakar Tülüce[32], Mehmet Kıs[32], Ahmet Gündeş[1], Emrah Yeşil[1], Özge Kurmuş[33], Şeyda Günay[33], Hamza Duygu[32], Özcan Başaran[34], Sinan İnci[35], Mehmet Ballı[36], Özgen Şafak[37], Tuğba Kemaloğlu Öz[6], Fatma Köksal[36], Barış Çelebi[38], Buğra Özkan[36], Murat Biteker[34], Ali Zorlu[7], Hasan Yücel[7], Yakup Altaş[39], Selim Topçu[40], Lütfü Aşkın[41], Kerem Özbek[39], Volkan Emren[42], Kaya Özen[43], Didem Ovla[44].

The cities involved in the collaboration: *[1]Mersin, [2]İstanbul, [3]Elazığ, [4]Samsun, [5]Amasya, [6]İstanbul, [7]Sivas, [8]İzmir, [9]Rize, [10]Malatya, [11]İstanbul, [12]İstanbul, [13]Şanlıurfa, [14]Ankara, [15]Gaziantep, [16]Konya, [17]İstanbul, [18]Tekirdağ, [19]Edirne, [20]Şırnak, [21]Sinop, [22]Kayseri, [23]Mersin, [24]Tekirdağ, [25]Ankara, [26]Ankara, [27]Mersin, [28]Afyon, [29]İzmir, [30]İstanbul, [31]Şanlıurfa, [32]İzmir, [33]Mersin, [34]Muğla, [35]Aksaray, [36]Mersin, [37]Burdur, [38]Mersin, [39]Diyarbakır, [40]Erzurum, [41]Erzurum, [42]Afyon, [43]Diyarbakır, [44]Mersin-*Turkey*

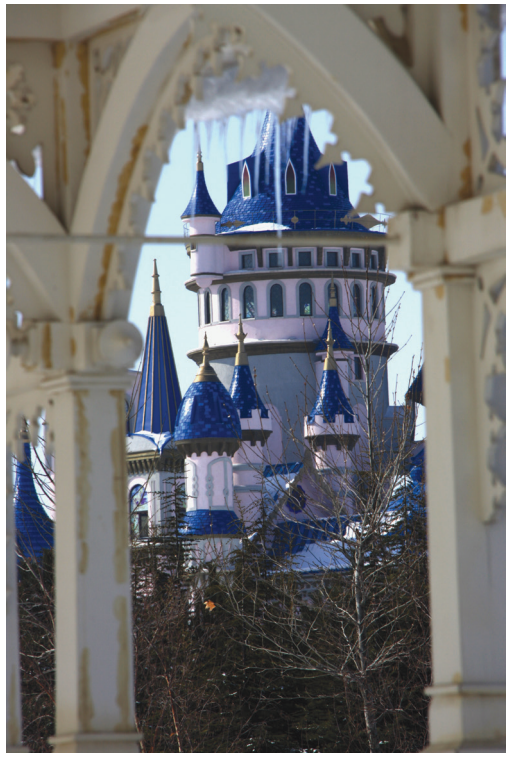
Conflict of interest: None declared.

Peer-review: Externally peer-reviewed.

References

1. Horton JD, Bushwick BM. Warfarin therapy: evolving strategies in anticoagulation. Am Fam Physician 1999; 59: 635-46.
2. Ansell J, Hirsh J, Hylek E, Jacobson A, Crowther M, Palareti G; American College of Chest Physicians. Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition) Chest 2008; 133: 160S-98S.
3. Jones M, McEwan P, Morgan CL, Peters JR, Goodfellow J, Currie CJ. Evaluation of the pattern of treatment, level of anticoagulation control, and outcome of treatment with warfarin in patients with non-valvar atrial fibrillation: a record linkage study in a large British population. Heart 2005; 91: 472-7.
4. Wallentin L, Yusuf S, Ezekowitz MD, Alings M, Flather M, Franzosi MG, et al. RE-LY investigators. Efficacy and safety of dabigatran compared with warfarin at different levels of international normalised ratio control for stroke prevention in atrial fibrillation: an analysis of the RE-LY trial. Lancet 2010; 376: 975-83.
5. Connolly SJ, Pogue J, Eikelboom J, Flaker G, Commerford P, Franzosi MG, et al. ACTIVE W Investigators. Benefit of oral anticoagulant over antiplatelet therapy in atrial fibrillation depends on the quality of international normalized ratio control achieved by centers and countries as measured by time in therapeutic range. Circulation 2008; 118: 2029-37.
6. White HD, Gruber M, Feyzi J, Kaatz S, Tse HF, Husted S, et al. Comparison of outcomes among patients randomized to warfarin therapy according to anticoagulant control: results from SPORTIF III and V. Arch Intern Med 2007; 167: 239-45.
7. Rosendaal FR, Cannegieter SC, van der Meer FJ, Briet E. A method to determine the optimal intensity of oral anticoagulant therapy. Thromb Haemost 1993; 69: 236-9.
8. Guyatt GH, Akl EA, Crowther M, Gutterman DD, Schuünemann HJ; American College of Chest Physicians Antithrombotic Therapy and Prevention of Thrombosis Panel. Executive summary: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012; 141(2 Suppl): 7S-47S.
9. Fuster V, Rydén LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, et al.; American College of Cardiology/American Heart Association Task Force on Practice Guidelines; European Society of Cardiology Committee for Practice Guidelines; European Heart Rhythm Association; Heart Rhythm Society. ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Com-

mittee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. Circulation 2006; 114: e257-354.
10. Pengo V, Pegoraro C, Cucchini U, Iliceto S. Worldwide management of oral anticoagulant therapy: the ISAM study. J Thromb Thrombolysis 2006; 21: 73-7.
11. Camm AJ, Lip GY, De Caterina R, Savelieva I, Atar D, Hohnloser SH, et al. ESC Committee for Practice Guidelines (CPG). 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. Eur Heart J 2012; 33: 2719-47.
12. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC Jr, et al. American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol 2014; 64: e1-76.
13. Konstantinides SV, Torbicki A, Agnelli G, Danchin N, Fitzmaurice D, Galiè N, et al. Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC). 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism. Eur Heart J 2014; 35: 3033-69.
14. Kernan WN, Ovbiagele B, Black HR, Bravata DM, Chimowitz MI, Ezekowitz MD, et al. American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, and Council on Peripheral Vascular Disease. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2014; 45: 2160-236.
15. Ertaş F, Kaya H, Yüksel M, Soydinç MS, Alan S, Ülgen MS. Atrial Fibrillation in Turkey: Epidemiologic Registry (AFTER) study design. Anadolu Kardiyol Derg 2013; 13: 339-43.
16. Ertaş F, Kaya H, Kaya Z, Bulur S, Köse N, Gül M, et al. Epidemiology of atrial fibrillation in Turkey: preliminary results of the multicenter AFTER study. Turk Kardiyol Dern Ars 2013; 41: 99-104.
17. Karaçağlar E, Atar I, Yetiş B, Corut H, Ersoy B, Yılmaz K, et al. The frequency of embolic risk factors and adequacy of antiembolic treatment in patients with atrial fibrillation: a single tertiary center experience. Anadolu Kardiyol Derg 2012; 12: 384-90.
18. Ertaş F, Duygu H, Acet H, Eren NK, Nazlı C, Ergene AO. Oral anticoagulant use in patients with atrial fibrillation. Turk Kardiyol Dern Ars 2009; 37: 161-7.
19. Pokorney SD, Simon DN, Thomas L, Fonarow GC, Kowey PR, Chang P, et al. Patients' time in therapeutic range on warfarin among US patients with atrial fibrillation: Results from ORBIT-AF registry. Am Heart J 2015; 170: 141-8.
20. Lindh JD, Andersson ML, Mannheimer B. Adherence to guidelines for avoiding drug interactions associated with warfarin-a Nationwide Swedish Register Study. PLoS One 2014; 9: e97388.



Biochemist, MD. Meral Egüz's collections, Fairy Tale Castle, Eskişehir