

# Potential Factors Affecting the Anticoagulation Control in Patients Treated with Warfarin: Results WARFARIN-TR Study

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## Abstract

**Background:** In the present study, we aimed to evaluate the factors that might be caused by adequate anticoagulation control in patients treated with warfarin for any reason. **Methods:** The WARFARIN-TR (The Awareness, Efficacy, Safety, and Time in Therapeutic Range of Warfarin in Turkish Population) study included 4987 patients using warfarin between January 1, 2014 and December 31, 2014. Time in therapeutic range (TTR) was calculated according to F. R. Roosendaal's algorithm with linear interpolation. The study population divided into two groups; adequate international normalized ratio (INR) control when TTR  $\geq 70\%$  (Group 1,  $n = 1068$ , 21.4%) and inadequate INR control when TTR  $< 70\%$  (Group 2,  $n = 3919$ , 78.6%). All demographic and clinic characteristics of the patients were compared to determine possible factors that might be cause adequate warfarin use. **Results:** The mean age of the study population was  $60.7 \pm 13.5$  years, and there was no significant difference between groups. The mean TTR value of Group 1 was significantly higher than Group 2 ( $80 \pm 8.5$  vs.  $40.9 \pm 17.2$ ;  $P < 0.001$ ). The traditional cardiovascular risk factors were similar between groups except hypertension (Group 1 51.4% and Group 2 56.4%;  $P = 0.004$ ) and chronic kidney disease (Group 1 8.3% and Group 2 5.5%;  $P = 0.001$ ). There were no significant differences between groups regarding bleeding. The awareness of warfarin use was significantly higher in Group 1 patients than Group 2 patients. Multivariate logistic regression analysis revealed that age (odds ratio [OR], 1.007;  $P = 0.014$ ), hypertension (OR, 0.821;  $P = 0.01$ ), atrial fibrillation (OR, 1.180;  $P = 0.033$ ), chronic kidney disease (OR, 1.697;  $P < 0.001$ ), to know warfarin use reason (OR, 1.699;  $P < 0.001$ ), and know to food-drug interaction with warfarin (OR, 1.583;  $P < 0.001$ ) were independent predictors of adequate coagulation. **Conclusion:** Our study demonstrated that a low proportion of patients taking warfarin achieve an adequate TTR in daily practice. Furthermore, the patients with adequate TTR are more aware of warfarin use.

**Keywords:** Adequate anticoagulation, warfarin, warfarin awareness

## INTRODUCTION

Warfarin is an effective oral anticoagulant which is used for the prevention of thromboembolic events especially in patients with atrial fibrillation (AF) and prosthetic valve. Warfarin reduces the stroke by 64% compared to the placebo in patients with AF, and it is the unique treatment for prosthetic valve patients.<sup>[1,2]</sup> The efficacy and safety of warfarin are dependent on maintenance of the international normalized ratio (INR). The target INR values alter according to the reason of warfarin use; the TTR should be above 70% for optimal efficacy and safety of warfarin use.<sup>[3-6]</sup> The risk of total mortality and major bleeding increases with TTR value below 70%.<sup>[3,5]</sup> However, many studies from Turkey

have shown that the number of patients with TTR value above 70% is very low in daily practice. Previous studies have shown that many factors may cause a low rate of TTR in different study populations.

In the present study, we aimed to evaluate the factors that might be caused by adequate anticoagulation control in patients treated with warfarin in the WARFARIN-TR (The Awareness,

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Efficacy, Safety, and Time in Therapeutic Range of Warfarin in Turkish Population) population study.

## METHODS

The design, conduct, and both main and subgroup results of the WARFARIN-TR study have been presented previously.<sup>[7-9]</sup> In brief, WARFARIN-TR study is a multi-center prospective observational study included 42 centers from 24 cities in seven regions of Turkey. Patients ( $n = 4987$ , mean age:  $60.7 \pm 13.5$  years, 44.9% male) attended follow-ups for 12 months. Of the total number of patients, 2124 (42.6%) had a mechanical valve, 1918 (38.4%) had nonvalvular AF, and 985 (19%) had other conditions as warfarin indications. The patients' data were recorded during routine clinic follow-up, and the INR values were recorded from the hospital records. The patients' INR data were extracted for the period of January 1, 2014–December 31, 2014. 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 safety and efficacy of warfarin therapy are dependent on maintaining the INR within the target is 2.5 (range 2.0–3.0) for patients with a mechanical aortic valve, nonvalvular 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.<sup>[10]</sup> TTR was calculated according to F. R. Roosendaal's algorithm with linear interpolation.<sup>[11]</sup>

For the hypothesis of the present study, we divided patients into two groups; adequate INR control when  $TTR \geq 70\%$  (Group-1,  $n = 1068$ , 21.4%) and inadequate INR control when  $TTR < 70\%$  (Group-2,  $n = 3919$ , 78.6%). All demographic and clinic characteristics of the patients were compared to determine possible factors that might be cause adequate warfarin use.

### Statistical analysis

The continuous variables were presented as mean  $\pm$  standard deviation, and the categorical variables were expressed as number and percentage (%). The continuous variables were compared with the Student's *t*-test or the Mann–Whitney U-test. Chi-square test or Fisher's exact test were used to compare categorical variables. The homogeneity of the variances was tested with Levene's test. To determine the independent predictors of  $TTR \geq 70\%$ , the logistic regression analysis was structured. The possible factors that identified with univariate analyses were entered into the logistic regression analysis. The Statistical Package for the Social Sciences (SPSS for Windows, Version 20.0, SPSS Inc., Chicago, IL, USA) was used for the statistical analysis.  $P < 0.05$  was determined as statistically significant.

## RESULTS

Of the 4987 patients included in the Warfarin-TR study, only one in fifth had adequate anticoagulation control (Group 1,  $n = 1068$ , 21.4%). Baseline demographic and clinical characteristics of the two groups are summarized in Table 1.

**Table 1: Baseline clinical and demographic characteristics of groups**

Variables	Group 1 ( $n=1068$ ), $n$ (%)	Group 2 ( $n=3919$ ), $n$ (%)	<i>P</i>
Age (year) and mean $\pm$ SD	60.6 $\pm$ 13.5	60.8 $\pm$ 13.3	0.638
Female	582 (54.5)	2167 (55.3)	0.641
TTR (%) and mean $\pm$ SD	80 $\pm$ 8.5	40.9 $\pm$ 17.2	<0.001
Number of INR monitoring 1 year and mean $\pm$ SD	10.3 $\pm$ 3.5	10.2 $\pm$ 2.8	0.294
Hypertension	549 (51.4)	2209 (56.4)	0.004
Diabetes mellitus	229 (21.4)	811 (20.7)	0.594
Current smoker	214 (20.0)	821 (20.9)	0.515
Hyperlipidemia	237 (22.2)	832 (21.2)	0.497
Atrial fibrillation	641 (60.0)	2231 (56.9)	0.070
Heart failure	242 (22.7)	979 (25.0)	0.118
Antiplatelet agent use	243 (22.8)	962 (24.5)	0.225
Coronary artery disease	240 (22.5)	916 (23.4)	0.536
Pulmonary embolism	53 (5.0)	196 (5.0)	0.959
Deep venous thrombosis	43 (4.0)	231 (5.9)	0.018
Cerebrovascular event	101 (9.5)	364 (9.3)	0.866
Chronic kidney disease	89 (8.3)	215 (5.5)	0.001
Following doctor (cardiologist)	1018 (95.3)	3611 (92.3)	<0.001
Any bleeding event	198 (18.4)	807 (20.6)	0.138
Major bleeding	33 (3.1)	12 (3.2)	0.869
Minor bleeding	165 (15.4)	682 (17.4)	0.132
Warfarin use reason			
NVAf	433 (40.5)	1485 (37.9)	0.078
MHV	456 (42.7)	1666 (42.5)	
Other	179 (16.8)	768 (19.8)	

MHV: Mechanical heart valve, NVAf: Nonvalvular atrial fibrillation, SD: Standard deviation, TTR: Time in therapeutic range, INR: International normalized ratio

The mean age of the study population was  $60.7 \pm 13.5$  years, and there was no significant difference between the two groups. The mean TTR value of Group 1 was significantly higher than Group 2 ( $80 \pm 8.5$  vs.  $40.9 \pm 17.2$ ;  $P < 0.001$ ). The traditional cardiovascular risk factors were similar between groups except hypertension (Group 1 51.4%, Group 2 56.4%;  $P = 0.004$ ) and chronic kidney disease (Group 1 8.3%, Group 2 5.5%;  $P = 0.001$ ). There were no statistically significant differences between groups regarding warfarin use reason. Although majority of the patients were followed by a cardiologist, the number of patients who followed by a cardiologist were significantly higher in Group 1 than Group 2 (95.3% vs. 92.3%;  $P < 0.001$ ). Even though any bleeding and minor bleeding events were higher in Group 2 than Group 1, it was not statistically significant. Furthermore, the major bleeding rate was similar between groups [Table 2]. The awareness of warfarin use which determined with three questions, known to use warfarin, known to the reason of warfarin use, and known to food-drug interactions with warfarin, was significantly higher in Group 1 than Group 2 [Figure 1]. Multivariate logistic regression analysis revealed that age (odds ratio [OR], 1.007; 95% confidence interval [CI], 1.002–1.013;  $P = 0.014$ ),

hypertension (OR, 0.821; 95% CI, 0.707–0.955;  $P=0.01$ ), AF (OR, 1.180; 95% CI, 1.014–1.374;  $P=0.033$ ), chronic kidney disease (OR, 1.697; 95% CI, 1.301–2.215;  $P < 0.001$ ), to known warfarin use reason (OR, 1.699; 95% CI, 1.341–2.153;  $P < 0.001$ ), and known to food-drug interaction with warfarin (OR, 1.583; 95% CI, 1.350–1857;  $P < 0.001$ ) were independent predictors of adequate coagulation [Table 3].

## DISCUSSION

Our study that reflecting daily practice determined that only one-fifth of the patients who use warfarin for any reason have adequate coagulation. In addition, the mean TTR value of groups was dramatically different. This result showed that the patients with adequate coagulation control had highly good control; however, the patients with inadequate coagulation have extremely poor control. Moreover, our results revealed that the awareness of warfarin use of patients with adequate coagulation was significantly higher than inadequate coagulation, and it is independent predictors of adequate coagulation.

**Table 2: Comparison of bleeding ratio between groups**

Bleeding type	Group 1 (n=1068), n (%)	Group 2 (n=3919), n (%)	P
Any bleeding event	198 (18.4)	807 (20.6)	0.138
Major bleeding	33 (3.1)	12 (3.2)	0.869
Minor bleeding	165 (15.4)	682 (17.4)	0.132

**Table 3: Predictors of time in therapeutic range  $\geq 70\%$  in multivariate logistic regression analysis**

Variable	OR	95% CI	P
Age	1.007	1.002-1.013	0.014
Hypertension	0.821	0.707-0.955	0.010
Atrial fibrillation	1.180	1.014-1.374	0.033
Chronic kidney disease	1.697	1.301-2.215	<0.001
To know warfarin use reason	1.699	1.341-2.153	<0.001
Know to food-drug interaction with warfarin	1.583	1.350-1857	<0.001

CI: Confidence interval, OR: Odds ratio

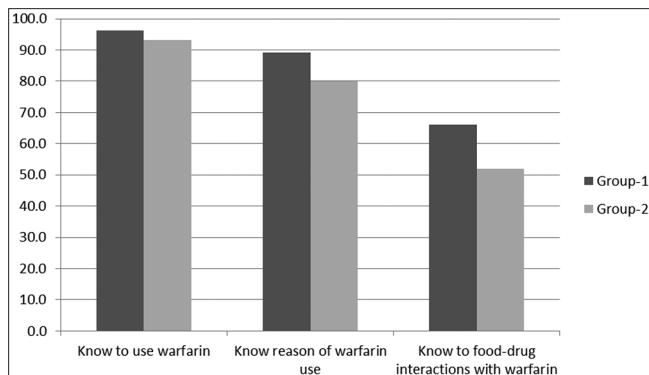


Figure 1: Comparison of awareness of warfarin use

Our results are fairly consistent with previous studies that conducted in Turkish patients.<sup>[12-14]</sup> In their study, Turk *et al.* reported that the mean TTR was 42.3%  $\pm$  18.4% in patients with valvular and nonvalvular AF. In the same study, 44% of patients had TTR <40%.<sup>[12]</sup> Ertaş *et al.* conducted a study that included 2242 patients with at least one AF episode reported that only 41.3% of all patients had adequate INR levels.<sup>[13]</sup> Furthermore, the study conducted by our group have shown that although mean TTR level was favorable in warfarin specialized outpatients clinic (68.8% $\pm$ 15.88), it was unfavorable in general cardiology outpatients clinic (51.6% $\pm$ 23.04).<sup>[14]</sup> Even though the mean TTR of general cardiology outpatient’s clinic is higher than other studies that conducted by Turk and Ertas, it is so far from adequate value. Furthermore, this study has shown the importance of follow-up clinic. In WARFARIN-TR study, we did not evaluate the effect of specialized and general outpatient’s clinic separately. However, we recorded the physician that follow-up patients. Although the majority of patients followed up by a cardiologist, the number in Group 1 was significantly higher than Group 2. Previous studies have shown that comorbidities such as diabetes mellitus, hypertension, and heart failure might be associated with inadequate TTR control.<sup>[15,16]</sup> On the contrary of previous studies, in this study, there were no significant differences between groups regarding traditional cardiovascular risk factors except hypertension and chronic kidney disease. Chronic kidney disease is an independent predictor of adequate coagulation. This might be explained by the patients with chronic kidney disease tightly follow-up by their physicians both for kidney function and warfarin use. On the other hand, hypertension is significantly higher in Group 2 that may explain by an explanatory mechanism is the possible interaction between warfarin and drugs administered to hypertension. The awareness of warfarin use is important in achieving the optimal TTR. As we emphasized, above the follow-up, clinics are play an important role in adequate coagulation.<sup>[14,17,18]</sup> Previous studies have shown that significantly higher TTR level is reached with INR specialized outpatient clinics rather than general clinics follow-up coagulation.<sup>[14,17,18]</sup> An advantage of INR specialized outpatient clinics is frequent reminding of food-drug interaction with warfarin that might result in better TTR value. In the present study, we showed that the awareness of warfarin use was an independent predictor of adequate coagulation. The safety and efficacy of warfarin therapy depend critically on maintaining the INR within the therapeutic range.<sup>[19-22]</sup> Many studies found that a vast number of bleeding events occurred when the INR was outside the therapeutic range.<sup>[22,23]</sup> Similarly, to the previous studies, in this study, the number of any bleeding and minor bleeding were higher in Group 2 than Group 1; however, it was not statistically significant. In contrast to the previous studies, the major bleeding rate was similar between groups. The low number of bleeding might be due to short follow-up periods of patients and also incomplete declarations of patients.

## CONCLUSION

Our study demonstrated that a low proportion of patients taking warfarin achieve an adequate coagulation in daily practice. Furthermore, patients with adequate coagulation were more aware of warfarin use.

## Limitations

The main limitation of our study was that we did not evaluate the stroke rate of the patient during the study period. Another limitation is that due to the study conducted in outpatient clinics, it might be caused by limited answers of patients in some busy outpatient clinics.

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## Conflicts of interest

There are no conflicts of interest.

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