Evaluation of Bleeding Rate and Time in Therapeutic Range in Patients Using Warfarin Before and During the COVID-19 Pandemic—Warfarin Treatment in COVID-19

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Abstract

The treatment process of patients using warfarin is expected to be hindered during the COVID-19 pandemic. Therefore we investigated whether the time in therapeutic range (TTR) and bleeding complications were affected during the COVID-19 pandemic. 355 patients using warfarin were included between March 2019 to March 2021. Demographic parameters, INR (international normalized ratio), and bleeding rates were recorded retrospectively. The TTR value was calculated using Rosendaal's method. The mean age of the patients was 61 ± 12 years and 55% of them were female. The mean TTR value during the COVID-19 pandemic was lower than the pre-COVID-19 period (56 ± 21 vs 68 ± 21, $P < 0.001$). Among the patients, 41% had a lack of outpatient INR control. During the COVID-19 pandemic, 71 (20%) patients using VKA suffered bleeding. Among patients with bleeding, approximately 60% did not seek medical help and 6% of patients performed self-reduction of the VKA dose. During the COVID-19 pandemic, TTR values have decreased with the lack of monitoring. Furthermore, the majority of patients did not seek medical help even in case of bleeding.

Introduction

Warfarin is the most common drug among vitamin K antagonists in the treatment of atrial fibrillation (AF), arterial and venous thrombosis, pulmonary embolism, and mechanical heart valves.[1] Warfarin exerts its anticoagulant effect by inhibiting vitamin K production, which is essential for the metabolism of certain coagulation factors.[2] Warfarin has a narrow therapeutic window. Furthermore, genetic factors, drugs, food interaction, and patient adherence hinder warfarin treatment. In this context, patients on warfarin treatment require strict follow-up and meticulous dose adjustment to avoid bleeding and thrombosis complications.[3] Warfarin dose should be controlled and adjusted with the International Normalized Ratio (INR), which has to be in a certain range according to the indication.[4] Apart from INR, clinicians usually calculate time in therapeutic range (TTR) levels to assess long-term INR changes. Based on the clinical evidence, TTR must be over 70%, which is the safest and most effective level for the treatment of thromboembolism.[5,6]

Severe acute respiratory syndrome coronavirus 2 (SARS-Cov2), which is responsible for the COVID-19 pandemic, has led to a great burden on hospital facilities and health services around the world. During the pandemic, many hospitals were overwhelmed because of the great number of hospitalized and ambulatory COVID-19 infected patients. Since the beginning

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of the pandemic, many governments have imposed complete or partial lockdown in their countries to constrain the transmission of SARS-Cov2. Therefore, many patients with cardiovascular disease might avoid health services when taking into account all these factors. On the other hand, some of them might be reluctant to be admitted to hospitals due to fear of contracting SARS-Cov2. In this regard, we aimed to investigate the changes in TTR level and bleeding complications in patients on warfarin treatment before and during the COVID-19 pandemic.

Methods

In this retrospective study, 355 patients on warfarin treatment were included between March 2019 and March 2021. Ethical approval was obtained, and the study was consistent with the principles of the Helsinki Declaration.

Patients' demographic data such as age, gender, indication of warfarin treatment, additional antiaggregant, concomitant diseases (cardiovascular disease, cancer, etc.), and use of non-steroidal anti-inflammatory drugs were acquired from the hospital database.

Indications for warfarin treatment were valvular AF (rheumatic moderate and severe mitral stenosis), non-valvular AF, mechanical heart valve, intracardiac thrombus, venous thrombosis, and pulmonary embolism. Exclusion criteria were as follows: younger than 18 years old, using warfarin less than 2 years, and pregnancy.

Hypertension was present if the patient was on hypertension treatment or had newly diagnosed hypertension with a consecutive blood measurement over 140/90 mmHg.[7] If the patient was on diabetes treatment or had fasting blood glucose over 126 mg/dl or HgA1c level over 6.5 gr/dl, they were considered as having diabetes mellitus (DM).[8] Patients were accepted as having a peripheral disease if the ankle-brachial index was lower than 0.9 or there was atherosclerotic stenosis at the carotid, vertebral, upper extremity, mesenteric, renal, or lower extremity arteries with Doppler ultrasonography, computed tomography, magnetic resonance angiography, or duplex subtraction angiography.[9] Stroke was determined based on past stroke or central cerebral damage due to cerebral infarct, or intracerebral or subarachnoid hemorrhage. Otherwise, if the neurologic condition resolved without obvious imaging findings, the patient was considered as having a transient ischemic attack (TIA).[10] Coronary artery disease was defined as 50% or more stenosis present in any of the coronary territory.[11] Patients were considered as having heart failure if the left ventricle ejection fraction was lower than 40% or preserved ejection fraction with echocardiographic, laboratory, and clinical findings suggestive of heart failure.[12] In addition, CHADS VASC score for patients with AF (Congestive heart failure, Hypertension, Age (>65 = 1 point, >75 = 2 points), DM, previous Stroke/TIA (2 points), vascular disease (peripheral arterial disease, previous myocardial infarction, aortic atheroma), female gender, and HAS-BLED score (hypertension, abnormal liver/renal function, stroke history, bleeding history or predisposition, labile INR, elderly, drug/alcohol usage) was calculated for all patients.[13]

We obtained at least 5 INR values from patients before and after the beginning of the COVID-19 pandemic on the 11th of March 2020 when the first case was reported in Turkey. The Rosendaal method was used to calculate TTR for all patients. During the COVID-19 pandemic, frequency of hospital admission, major and minor, and clinically non-relevant major (CRNM) bleeding rates were asked of patients and searched in the hospital database.

According to the International Society On Thrombosis and Hemostasis (ISTH) criteria, major bleeding was defined as fatal bleeding and/or bleeding in critical areas and organs such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular, pericardial, and intramuscular part or hemoglobin decrease of more than 2 g/dl or needing 2 and more units of erythrocyte or whole blood transfusion. CRNM bleeding was defined as a requirement for medical intervention, needing hospitalization, or leading physician-guided intervention. Other bleedings that were not compatible with major or CRNM bleeding were accepted as minor bleeding.[14,15]

Statistical Analysis

Statistical analyzes were conducted using SPSS software version 23.0. Variables were analyzed using visual and analytical methods to determine normal distribution. Continuous and categorical variables were expressed as mean and standard deviation or percentages, respectively. Paired t-test was used to compare TTR changes before and during the COVID-19 period. A one-way ANOVA test was used to compare TTR values between groups separated by warfarin indications. Univariate and multivariate logistic regression analysis was used to assess independent predictors for bleeding. A 2-sided P-value <0.05 was considered statistically significant.

Results

The mean age of the patients was 61 ± 12 years and the study population was predominantly female gender (55%). Indications for VKA use were as follows: mechanical heart valve (74%), valvular AF (18%), non-valvular AF (7%), intracardiac thrombus (1%), and pulmonary embolism (1%). Baseline characteristics of the patients are shown in Table 1.

The mean TTR value was lower during the COVID-19 pandemic than the pre-COVID-19 period (56 ± 21 vs 68 ± 21, P < 0.001). Regarding warfarin indications, the TTR value was decreased significantly during the COVID-19 pandemic in all groups (Figure 1). TTR changes before and during COVID-19 were not different between patients with valvular AF (-8.8 ± 25), non-valvular AF (-13 ± 19), and mechanical heart valve (-12 ± 22) ($P = 0.485$) (Figure 2).

During the COVID-19 pandemic, 71 (20%) patients using VKA suffered bleeding. Only 2 patients experienced both major and CRNM bleeding, whereas other patients developed CRNM and minor bleeding. The most common CRNM

bleeding was epistaxis, bruising, gingival bleeding, and hematuria (Table 2). Among patients with bleeding, approximately 60% did not seek medical help, 6% of patients performed self-reduction of VKA dose, and the remaining 34% of patients were admitted to a physician. In addition, 41% of patients had a lack of outpatient INR control.

Table 1. Baseline Characteristics of the Patients Using Vitamin K Antagonists.

Age, years	61 ± 12
Female gender	196 (55%)
Hypertension	126 (35%)
Diabetes mellitus	72 (20%)
Heart failure	30 (8%)
Stroke/TIA	28 (8%)
Alcohol use	none
Coronary artery disease	38 (11%)
Peripheral artery disease	2 (1%)
Cancer	6 (2%)
Hemoglobin g/dl	12.6 ± 1.6
Platelets $\times 10^9$/L	246 ± 67
AST U/L	25 ± 34
ALT U/L	20 ± 12
Creatinine mg/dl	0.97 ± 0.5
GFR ml/min/1.73 m^2	58 ± 11
NSAID use	33 (9%)
Additional drug	18 (5%)
Indication of Vitamin K antagonist	
Non-valvular AF	26 (7%)
Valvular AF	63 (18%)
Mechanical valve	262 (74%)
Intracardiac thrombus	2 (1%)
Pulmonary embolism	2 (1%)

After univariate analysis, coronary artery disease (HR (Hazard Ratio): 4.966 (95%CI (Confidence Interval): 2.180-11.312, $P < 0.001$), cancer HR: 9.438 (95%CI: 1.471-60.560, $P = 0.018$), and HAS-BLED score HR: 1.662 (95%CI: 1.240-2.226, $P = 0.001$) were independent predictors of bleeding in multivariate analysis (Table 3).

Discussion

In this study, we investigated the bleeding rates and changes of TTR in patients using warfarin during the COVID-19 pandemic. According to this study, the mean TTR value was lower during the COVID-19 pandemic than the pre-COVID-19 period (56 vs 68, $P < 0.001$). Among the patients, 41% had a lack of outpatient INR control. During the COVID-19 pandemic, 71 (20%) patients using VKA suffered bleeding. Among patients with bleeding, approximately 60% did not seek medical help, 6% of patients performed self-reduction of VKA dose, and the remaining 34% of patients applied to physicians.

During the COVID-19 pandemic, especially in the beginning period, the facilities of hospitals and outpatient clinics were mainly used for COVID-19 patients. Outpatient clinical services were restricted to those with ambulatory patients with cardiovascular disease. Patients were also concerned about hospitals and outpatient clinics being an easy source of virus transmission. Putting all these factors together, it was likely that the number of visits of patients using warfarin was decreased. Thus, 41% of patients had a lack of hospital admission. Nevertheless, the TTR value was higher than previous studies that were conducted with the Turkish population, despite having decreased in the COVID-19 period. Turk et al showed that the mean TTR value was about 42% in patients
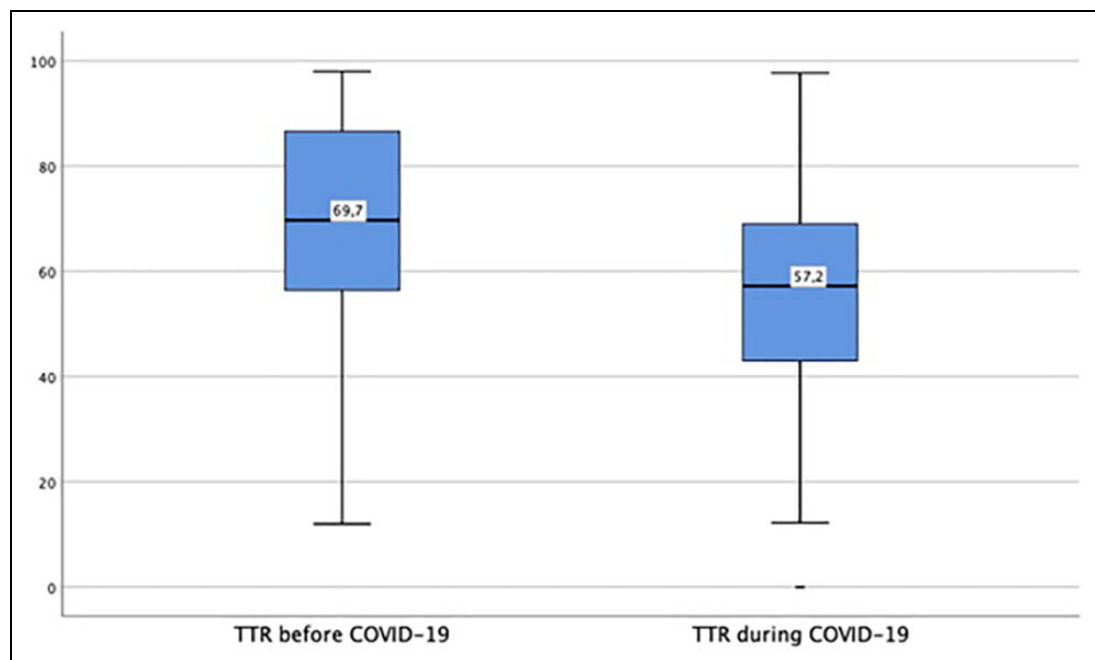

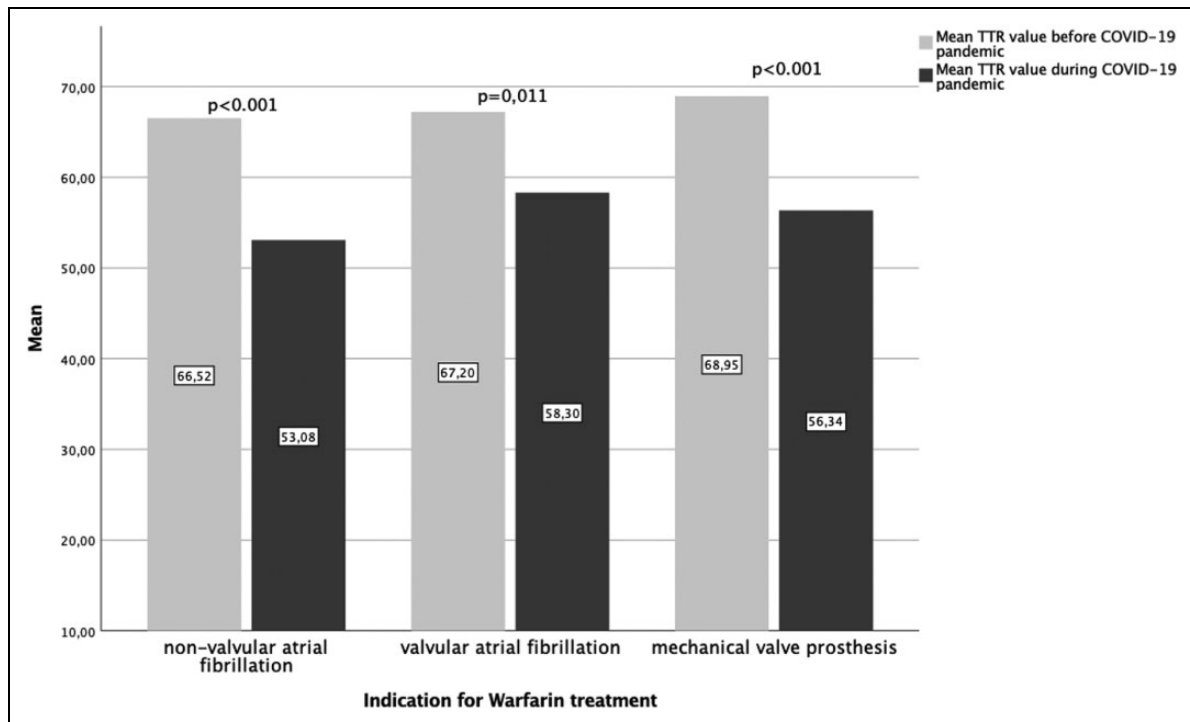**Figure 1.** TTR values before and during the COVID-19 pandemic.

Figure 2. TTR changes before and during the COVID-19 pandemic in patients with non-valvular, valvular and mechanical heart valves.

Table 2. Bleeding Rates of Patients Using Warfarin During the COVID-19 Pandemic.[a]

Bleeding	71 (20%)
Major bleeding	2 (1%)
CRNM and minor bleeding	
Hematuria	12 (17%)
Epistaxis	20 (28%)
Retinal hemorrhage	2 (3%)
Hematoma	2 (3%)
Bruising	14 (20%)
Hemoptysis	2 (3%)
Hematemesis	3 (4%)
Gingival bleeding	12 (17%)
Hemorrhoidal bleeding	2 (3%)
Other	2 (3%)

Abbreviations: CRNM, clinically non-relevant major.
[a]Percentages are given for patients with bleeding.
[b]CHA$_2$DS$_2$-Vasc was not included in multivariate logistic regression, since many variables were present in the CHA$_2$DS$_2$-Vasc and HAS-BLED score.

with valvular and non-valvular AF.[16] Ertaş et al reported that among patients with valvular and non-valvular AF only 41% of patients were in the normal therapeutic range.[17] In the Warfarin-TR study, the mean TTR value was around 50% in patients with valvular and non-valvular AF. Many factors might have a role in why the TTR values were still higher than in previous studies. One of the possible explanations is that our study population was mainly composed of patients with a mechanical valve and valvular AF. However, a great number of non-valvular AF patients were included in previous studies conducted in Turkey. It was shown that non-valvular AF patients have a lower awareness of warfarin use and TTR values compared to those with valvular AF.[18] Furthermore, non-valvular AF patients had less drug adherence even under treatment with novel oral anticoagulants.[19] The mean TTR value was higher in patients with valvular AF than those with non-valvular AF in this study.

In our study, bleeding rates under warfarin treatment were similar to previous studies.[18] However, the duration of the study period was shorter than the previous studies. Lack of monitoring and TTR values did not affect bleeding outcomes. Coronary artery disease, cancer, and HAS-BLED score were independent predictors of bleeding. Patients with coronary artery disease had a higher probability of using antiaggregant drugs. These patients might have tended to bleed.

Since it is not known how long the current COVID-19 pandemic will last, patients with warfarin treatment may still avoid ambulatory visits and INR monitoring. For patients needing long-term warfarin treatment such as those with a mechanical heart and valvular atrial fibrillation may be provided self-monitoring of the INR program with a hand-held device.[20] However, costs and economic burden for patients should be kept in mind as these devices are not included in reimbursement programs in many countries. Also, health workers can visit these patients at home regularly to obtain a blood test for INR monitoring. Other groups of patients, especially those using warfarin for non-valvular AF, may be followed at home by changing warfarin to novel oral anticoagulants. These patients may be checked regularly with remote monitoring by telephone or internet-based systems.

Table 3. Independent Predictors of Bleeding in Univariate and Multivariate Logistic Regression Analysis.

	Univariate analysis				Multivariate analysis			
	HR	95% CI		P	HR	95% CI		P
Age	1.011	0.988	1.034	0.357				
Female gender	1.223	0.721	2.072	0.455				
Hypertension[a]	2.565	1.510	4.357	<0.001				
Diabetes Mellitus	2.101	1.167	3.785	0.013	1.454	0.750	2.817	0.268
Heart failure	1	0.393	2.547	1				
Stroke/TIA[a]	2.423	1.065	5.509	0.035				
Coronary artery disease	3.464	1.709	7.022	0.001	4.966	2.180	11.312	<0.001
Cancer	8.418	1.510	46.923	0.015	9.438	1.471	60.569	0.018
Hemoglobin g/dl	0.817	0.695	0.961	0.015	0.927	0.765	1.124	0.441
Platelets $\times 10^9$/L	1.003	0.999	1.007	0.141				
AST U/L	0.993	0.973	1.014	0.513				
ALT U/L	0.979	0.948	1.011	0.192				
GFR[a] ml/min/1.73 m^2	0.964	0.948	0.980	<0.001				
NSAID use[a]	2.183	1.005	4.745	0.049				
Additional drug	1.151	0.367	3.611	0.809				
Indication of VKA	0.281	0.090	0.884	0.030	0.269	0.070	1.028	0.055
Valvular AF								
TTR < 70	1.670	0.850	3.282	0.137				
CHA$_2$DS$_2$-VASc score[b]	1.233	1.054	1.441	0.009				
HAS-BLED score	1.691	1.316	2.173	<0.001	1.662	1.240	2.226	0.001
Lack of outpatient clinic application	1.411	0.837	2.381	0.197				

Abbreviations: AF, Atrial fibrillation; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; TTR, Time in therapeutic range; VKA, Vitamin K antagonists; CI, Confidence Interval; HR: hazard Ratio; HAS-BLED, Hypertension, Abnormal liver/renal function, Stroke history, Bleeding history or predisposition, Labile INR, Elderly, Drug/alcohol usage; CHA$_2$DS$_2$-VASc score, Congestive heart failure, Hypertension, Age (> 65 = 1 point, > 75 = 2 points), Diabetes, previous Stroke/transient ischemic attack (2 points), Vascular disease (peripheral arterial disease, previous myocardial infarction, aortic atheroma), and female gender.
[a]GFR (Glomerular Filtration Rate), Hypertension, Stroke/TIA (Transient Ischemic Attack), NSAID (Non-steroidal anti-inflammatory drugs) were not included in multivariate logistic regression analysis since these variables were included in the HAS-BLED score.

Limitations of the Study

This was a retrospective study conducted in a single center. Nevertheless, bleeding complications and demographic variables were double-checked by asking the patient and going through hospital records. There might be a lack of information on the clinical data of the patients. Given that the COVID-19 pandemic is still ongoing, this study could report almost a 1-year period of TTR and bleeding rates. Nevertheless, we may need to follow the long-term effect of this pandemic on TTR and bleeding rates.

Conclusions

The overwhelming effect of the COVID-19 pandemic on the health care system may hamper the treatment of warfarin-treated patients. In addition, these patients may be lacking in INR control. In this regard, TTR values of warfarin-treated patients have significantly decreased since the beginning of COVID-19, which in turn makes these patients vulnerable to bleeding complications.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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