The treatment indication affects the time in therapeutic range

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ABSTRACT

Objectives: This study aimed to compare the efficacy and safety of the treatment in patients with deep vein thrombosis (DVT) and mechanical mitral valve replacement (MVR) who were treated with warfarin for different indications.

Patients and methods: A total of 536 patients (314 males, 222 females; mean age: 55.6±10.8 years; range, 18 to 89 years) were retrospectively reviewed between January 2016 and January 2020. The patients were evaluated in two groups: 273 DVT patients (149 males, 124 females; mean age: 56.7±11.3 years) who received long-term therapy (six months) and 263 mechanical MVR patients (165 males, 98 females; mean age: 56.2±9.4 years). Both groups were compared in terms of the percentage of time in the therapeutic range (TTR), the time to reach the target international normalized ratio (INR), and warfarin related complications.

Results: The number of total hospital visits and total INR measurements for six months in the MVR group was statistically significantly higher than in the DVT group (p<0.001). The duration and percentage of TTR in the first three and six months of the MVR group were statistically significantly higher than the DVT group (p<0.05).

Conclusion: More MVR patients remained in the therapeutic range than DVT patients due to the frequent hospital visits of these patients for various reasons; thus, it may be beneficial to increase the frequency of follow-up examinations or measurements of INR in patients who have started warfarin treatment for an indication other than valve replacement.

Keywords: Anticoagulants, deep venous thrombosis, heart valve prosthesis, therapeutic range, warfarin.

The most recognized way to measure the therapeutic effectiveness and quality of warfarin treatment over time is to measure the percentage of time in the therapeutic range (TTR).\cite{1} It has been shown that high TTR rates are associated with a lower risk of complications in terms of bleeding in patients using warfarin.\cite{2}

Deep vein thrombosis (DVT) patients often go to the hospital only for international normalized ratio (INR) control. However, patients with mechanical valve replacement (MVR) frequently apply to the hospital for wound evaluation and routine cardiac examinations, particularly in the first postoperative month. Therefore, this increases the number of clinical visits of patients. In this study, we predicted that the group with a higher number of hospital visits could potentially have better TTR rates.

When the literature was reviewed, there was no study comparing venous thrombus patients and patients who underwent mechanical valve replacement in terms of anticoagulation quality and complications. Hence, DVT and MVR patients were compared in terms of the percentages of TTR and supratherapeutic INR-related bleeding complications, aiming to compare the efficacy and safety of the treatment in patients who received warfarin for different indications.

PATIENTS AND METHODS

This retrospective study was conducted with 536 patients (314 males, 222 females; mean age: 55.6±10.8 years; range, 18 to 89 years) on oral anticoagulation with warfarin at the Katip Çelebi University, Faculty of Medicine, Department of Cardiovascular Surgery between January 2016 and January 2020. Data obtained from the hospital registry system. The patients were evaluated in two
groups: 273 DVT patients (149 males, 124 females; mean age: 56.7±11.3 years) who received long-term therapy (six months) and 263 mechanical MVR patients (165 males, 98 females; mean age: 56.2±9.4 years). Both groups were compared in terms of the percentage of TTR, the time to reach the target INR, and warfarin-related complications. Both groups were followed up by our team in our anticoagulation clinic for the first six months. Data including the initial demographic and clinical characteristics of the patients, INR measurements, number of clinical visits over a six-month period, and the number of INR measurements performed over a six-month period were recorded. In line with the recommendations of the literature, the target INR range was accepted as 2.0 to 3.0 in DVT patients, and the target INR range was accepted as 2.5 to 3.5 in patients with mechanical MVR.\cite{3,4} The TTR was calculated using the Rosendaal linear interpolation method.\cite{5} Inclusion criteria were patients who received anticoagulant therapy by indication of isolated mechanical MVR or venous thromboembolism. Exclusion criteria were patients with chronic renal failure or hypercoagulability syndrome, and cancer patients receiving chemotherapy. Patients were excluded if the INR was measured less frequently than once every two months in both groups. In addition, patients who underwent redo surgery in the mechanical valve group were excluded.

The definition of the complication was patients hospitalized with Grade 2 or higher bleeding according to the World Health Organization (WHO) Bleeding Scale due to supratherapeutic INR.\cite{6} Comparing the complications associated with the subtherapeutic INR was not suitable for this study as it was not fair to compare valve complications with recurrent DVT.

Blood product transfusion was decided according to previously published studies.\cite{4,7,8} Accordingly, fresh frozen plasma and erythrocyte suspension replacement was performed in patients with supratherapeutic INR (INR >5) and bleeding higher than Grade 2 according to the WHO Bleeding Scale.

**Statistical analysis**

All analyses were performed using IBM SPSS version 22.0 software (IBM Corp., Armonk, NY, USA). Descriptive statistics were calculated for baseline characteristics of patients. Kolmogorov-Smirnov and Shapiro-Wilk tests were employed to test the normality of data. Continuous variables were described as mean ± standard deviation, and categoric variables were presented as counts (percentages). We tested factors in univariate analyses (t-test and chi-square test). A p value <0.05 was considered statistically significant.

**RESULTS**

No statistically significant difference was found between the groups in terms of age, sex, smoking, arterial hypertension, diabetes mellitus, and prior cerebrovascular events (Table 1).

The number of total INR measurements for six months in the MVR group was statistically significantly higher than in the DVT group (p<0.001, Table 2). In addition, the number of total

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Patient demographics and clinical features</th>
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<td>DVT group (n=273)</td>
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<td>Age (year)</td>
<td>56.7±11.3</td>
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<td>Male</td>
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<td>Cerebrovascular events</td>
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DVT: Deep vein thrombosis; MVR: Mitral valve replacement; SD: Standard deviation.
hospital visits for six months in the MVR group was statistically significantly higher than in the DVT group (p<0.001, Table 2).

The mean TTR in the first three months in the DVT group was 46.6±18.3 days. The percentage of TTR in the first three months was 51.8%. In the same group, the mean TTR in the first six months was 106.0±26.7 days, and the TTR percentage was 58.9%. The mean TTR and percentage of the first three and six months in the MVR group were 49.7±16.8 days, 55.6% and 116.0±28.7 days, 64.8%, respectively. Thus, the duration and percentage of TTR in the first three and six months of the MVR group were statistically significantly higher than the DVT group (p<0.05, Table 2).

When the DVT group (n=54, 19.8%) and MVR group (n=49, 18.6%) were compared in terms of hospitalization history due to supratherapeutic INR, there was no statistically significant difference between the groups (Table 2). When the patients hospitalized due to supratherapeutic INR were evaluated, Grade 2 and higher bleeding was detected according to the WHO Bleeding Scale in seven (2.5%) patients in the DVT group and eight (3.0%) patients in the MVR group, and no statistically significant difference was found between the groups (Table 2). Additionally, the blood transfusion rate and the number of transfused blood products did not differ significantly in both groups (Table 2).

### DISCUSSION

Prior studies have reported strong associations between TTR and the efficiency and safety of the treatment. One of the basic principles behind keeping the TTR percentage high is undoubtedly patient compliance. Since the preoperative, operative, and postoperative processes for heart valve replacement patients are much more demanding than those for DVT patients, we designed this study based on the assumption that treatment compliance may be better in these patients. Therefore, to compare the efficacy and safety of warfarin treatment in DVT and prosthetic mitral valve patient groups were compared in terms of TTR percentage and complication rates.

It is a known fact that the demographic characteristics of the patients are associated with effective anticoagulation. In our study, we evaluated both patient groups in terms of demographic data, and we could not find a statistically significant difference between the groups. The homogeneity of the demographic data made the results of the study valuable.
There are limited studies examining the TTR percentages of patients using warfarin for different indications. However, there are no comparisons of different indications in these studies. In one of these studies, the median TTR percentage in DVT patients using warfarin was reported as 71.1%.[14] In another study, the median TTR percentage was reported to be 60% in patients with mechanical prosthetic valves.[15] In our study, both the first three-and six-month TTR percentages in the MVR group were found to be statistically significantly higher than those in the DVT group. One of the main reasons is that the prosthesis valve operation process is much more demanding than the DVT treatment process, so patient compliance is likely to be higher. In our opinion, another reason is that MVR patients require more hospital visits than the DVT group. In our study, when patient groups were evaluated in terms of total hospital admissions during the six-month follow-up, there was a statistically significantly higher number of admissions in the MVR group. While DVT patients mostly went to the hospital for INR control alone, MVR patients were frequently admitted for wound site evaluation and cardiac routine examinations, particularly in the first postoperative month. In addition, it was understood from the outpatient clinic registry system that these patients were immediately admitted to the hospital even with noncardiac infectious or noninfectious symptoms.

There are reported results regarding the relationship between TTR and bleeding complications. It was reported that the rate of major bleeding complications was reported between 1.0 and 2.36 in 100 patients using warfarin.[14,15] In the study of Kavasoglu et al.,[16] which included 415 patients using warfarin, the rate of major bleeding was reported as 2.6%.

When evaluated in terms of bleeding and complications related to supratherapeutic INR in our study, there was no statistically significant difference between the groups. However, the mean TTR percentages of patients with bleeding complications in both groups were below 60% both in three months and six months, and these results were consistent with the literature.[9] Being outside of the TTR does not necessarily lead to complications. There are patients with high INR who were incidentally discovered in our follow-ups and did not have any symptoms or complications. Therefore, although there is a serious correlation between being out of TTR and the incidence of complications, this will not be an absolute relationship. We think that this is the reason there was no statistically significant difference between the groups in this sense.

When the groups were evaluated independently, it was observed that the TTR percentage in the first six months was higher in both groups compared to the first three months. This led us to think that the time elapsed since the initiation of treatment increased the TTR percentage. Therefore, these findings can be interpreted as indicating that the quality of warfarin therapy is largely dependent on the time elapsed since the initiation of therapy.

The number of INR measurements may have been effective in the emergence of the statistically significant difference regarding the TTR percentages stated above. In the WARFARIN-TR study conducted in our country, patients monitored for one year with an INR ≤8 (n=1,752) were reported to have statistically significantly lower TTR levels than those with an INR >8.[17] In our study, in accordance with the literature, the number of total INR measurements for six months in the MVR group was statistically significantly higher than in the DVT group.

One of the reasons for the better TTR percentage in the MVR group can be attributed to the knowledge of or familiarity with therapy, which are a large part of treatment compliance. It was reported that patients who had a low level of knowledge regarding warfarin therapy experienced more problems in terms of their adherence to the medication.[18] Although most of the MVR patients were discharged with the subtherapeutic INR, they were already on medication at discharge. In other words, this was not the first time they used warfarin when they left the hospital. When viewed from this aspect, this may have caused a difference in the patient groups in terms of acceptance of the disease and compliance with treatment.

There are several limitations to this study. The study group consisted of a relatively small sample size compared to large registers. The study was planned in a retrospective manner. Furthermore, we did not have enough data on possible confounder variables, such as educational status, personal income data, occupation, and caregiver availability, which may have affected our results.

In conclusion, we found that more MVR patients remained in the therapeutic range than
DVT patients due to the high awareness of therapy process influenced by the difficulty of the MVR procedure and the frequent hospital visits of these patients. Therefore, it may be beneficial to increase the frequency of follow-up examinations or measurements of INR in patients who have started warfarin treatment for an indication other than valve replacement. Studies with larger sample sizes, different warfarin usage indications, and expanded sets of sociocultural demographic data of patients will provide further clarification.

Ethics Committee Approval: The study protocol was approved by the Katip Celebi University Faculty of Medicine Ethics Committee (Date/no: 19/11/2020–GÖKAE–0609). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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