Cardiovasc Surg Int 2022;9(3):147-151
http://dx.doi.org/DOI: 10.5606/e-cvsi.2022.1392
www.e-cvsi.org

Cardiovascular Surgery and Interventions

Original Article Open Access

The treatment indication affects the time in therapeutic range

Hasan İner

Department of Cardiovascular Surgery, Katip Çelebi University, Faculty of Medicine, Izmir, Türkiye

Received: August 13, 2022 ***Accepted:*** September 06, 2022 ***Published online:*** October 14, 2022

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).[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.[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

Corresponding author: Hasan İner, MD. Katip Çelebi Üniversitesi Tıp Fakültesi Kalp ve Damar Cerrahisi Anabilim Dalı, 35620 Çiğli, İzmir, Türkiye.
Tel: +90 553 - 132 51 10 e-mail: hasan_iner@hotmail.com

Citation:
İner H. The treatment indication affects the time in therapeutic range. Cardiovasc Surg Int 2022;9(3):147-151.

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.[3,4] The TTR was calculated using the Rosendaal linear interpolation method.[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.[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.[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 1
Patient demographics and clinical features

	DVT group (n=273)			MVR group (n=263)			
	n	%	Mean±SD	n	%	Mean±SD	p
Age (year)			56.7±11.3			56.2±9.4	0.476
Sex							0.055
Female	124	45.4		98	37.3		
Male	149	54.6		165	62.7		
Smoking	67	24.5		58	22.1		0.496
Hypertension	55	20.1		63	24.0		0.287
Diabetes mellitus	22	8.1		23	8.7		0.774
Cerebrovascular events	9	3.3		13	4.9		0.989

DVT: Deep vein thrombosis; MVR: Mitral valve replacement; SD: Standard deviation.

Table 2
Three-and six-month follow-up results

	DVT group (n=273)			MVR group (n=263)			
	n	%	Mean±SD	n	%	Mean±SD	*p*
Total INR counts, in six months			4.40±0.72			5.06±0.91	***<0.001
Total hospital visit counts, in six months			4.41±0.71			5.20±0.88	***<0.001
TTR, in three months			46.6±18.3			49.7±16.8	*0.046
Percentage of TTR, in three months			51.8±20.3			55.6±18.8	*0.026
TTR, in six months			106.0±26.7			116.0±28.7	***<0.001
Percentage of TTR, in six months			58.9±14.8			64.8±16.0	***<0.001
Complication	54	19.8		49	18.6		0.736
WHO Bleeding Scale Grade ≥2	7	2.5		8	3.0		0.737
Blood transfusion	27	10.3		23	8.4		0.464
FFP (units)			3.0±1.6			2.8±1.7	0.420
ES (units)			2.7±1.4			1.7±0.6	0.061

SD: Standard deviation; INR: International normalized ratio; TTR: Time in Therapeutic Range; WHO: World Health Organization; FFP: Fresh Frozen Plasma; ES: Erythrocyte Suspension.

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.[1,9,10] One of the basic principles behind keeping the TTR percentage high is undoubtedly patient compliance.[11] 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.[12,13] 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 Çelebi University Faculty of Medicine Ethics Committee (Date/no: 19/11/2020-GOKAE-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.

Conflict of Interest: The author declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding: The author received no financial support for the research and/or authorship of this article.

REFERENCES

1. Ansell J, Hirsh J, Hylek E, Jacobson A, Crowther M, Palareti G. Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008;133(6 Suppl):160S-198S.
2. Wieloch M, Själander A, Frykman V, Rosenqvist M, Eriksson N, Svensson PJ. Anticoagulation control in Sweden: Reports of time in therapeutic range, major bleeding, and thrombo-embolic complications from the national quality registry AuriculA. Eur Heart J 2011;32:2282-9.
3. Mazzolai L, Aboyans V, Ageno W, Agnelli G, Alatri A, Bauersachs R, et al. Diagnosis and management of acute deep vein thrombosis: A joint consensus document from the European Society of Cardiology working groups of aorta and peripheral vascular diseases and pulmonary circulation and right ventricular function. Eur Heart J 2018;39:4208-18.
4. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP 3rd, Guyton RA, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: Executive summary: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2014;129:2440-92.
5. Rosendaal FR, Cannegieter SC, van der Meer FJ, Briët E. A method to determine the optimal intensity of oral anticoagulant therapy. Thromb Haemost 1993;69:236-9.
6. Heddle NM, Wu C, Vassallo R, Carey P, Arnold D, Lozano M, et al. Adjudicating bleeding events in a platelet dose study: Impact on outcome results and challenges. Transfusion 2011;51:2304-10.
7. Carson JL, Stanworth SJ, Alexander JH, Roubinian N, Fergusson DA, Triulzi DJ, et al. Clinical trials evaluating red blood cell transfusion thresholds: An updated systematic review and with additional focus on patients with cardiovascular disease. Am Heart J 2018;200:96-101.
8. Holbrook A, Schulman S, Witt DM, Vandvik PO, Fish J, Kovacs MJ, et al. Evidence-based management of anticoagulant therapy: Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of chest physicians evidence-based clinical practice guidelines. Chest 2012;141(2 Suppl):e152S-e184S.
9. Phillips KW, Ansell J. Outpatient management of oral vitamin K antagonist therapy: Defining and measuring high-quality management. Expert Rev Cardiovasc Ther 2008;6:57-70.
10. Rose AJ, Hylek EM, Ozonoff A, Ash AS, Reisman JI, Berlowitz DR. Risk-adjusted percent time in therapeutic range as a quality indicator for outpatient oral anticoagulation: Results of the Veterans Affairs Study to Improve Anticoagulation (VARIA). Circ Cardiovasc Qual Outcomes 2011;4:22-9.
11. Ewen S, Rettig-Ewen V, Mahfoud F, Böhm M, Laufs U. Drug adherence in patients taking oral anticoagulation therapy. Clin Res Cardiol 2014;103:173-82.
12. Go AS, Fan D, Chang Y, Chan J, Lieu TA, Magid DJ, et al. Abstract 14870: Quality of anticoagulation management in atrial fibrillation and venous thromboembolism: The CVRN WAVE study. Circulation 2010;122:A14870.
13. Fauchier L, Poli D, Olshansky B. The SAMe-TT2R2 score and quality of anticoagulation in AF: Can we predict which patient benefits from anticoagulation? Thromb Haemost 2015;114:657-9.
14. Sandén P, Renlund H, Svensson PJ, Själander A. Bleeding complications in venous thrombosis patients on well-managed warfarin. J Thromb Thrombolysis 2016;41:351-8.
15. Poli D, Antonucci E, Pengo V, Migliaccio L, Testa S, Lodigiani C, et al. Mechanical prosthetic heart valves: Quality of anticoagulation and thromboembolic risk. The observational multicenter PLECTRUM study. Int J Cardiol 2018;267:68-73.
16. Kavasoğlu K, Kervan Ü, Sert DE, Kocabeyoğlu SS, Karahan M, Aygün E, et al. Patient and healthcare provider burden due to conventional measurement of the international normalized ratio: From a multi-dimensional perspective. Cardiovascular Surgery and Interventions 2021;8:70-7.
17. Çelik A, İzci S, Kobat MA, Ateş AH, Çakmak A, Çakıllı Y, et al. The awareness, efficacy, safety, and time in therapeutic range of warfarin in the Turkish population: WARFARIN-TR. Anatol J Cardiol 2016;16:595-600.
18. Demir Korkmaz F, Okgun Alcan A, Karacabay K. Do patients with mechanical heart valves have the appropriate knowledge regarding warfarin therapy and can they adhere to the correct dosage? Turk Gogus Kalp Dama 2015;23:58-65.