TJVS Turkish Journal of Vascular Surgery

Turk J Vasc Surg 2024;33(3):127-31
DOI: 10.9739/tjvs.2024.05.020

Available online at www.turkishjournalofvascularsurgery.org

Original Article

Analysis of early results of edoxaban and warfarin in the treatment of deep vein thrombosis

Abdullah Guner[1], Volkan Burak Taban[2], Muhammet Talha Ceran[1], Yuksel Dereli[3]

[1]Konya City Hospital, Department of Cardiovascular Surgery, Konya, Türkiye
[2]Şırnak State Hospital Department of Cardiovascular Surgery, Şırnak, Türkiye
[3]Necmettin Erbakan University, Meram Medical Faculty, Cardiovascular Surgery Clinic, Konya, Türkiye

Received: May 21, 2024 Accepted: August 05, 2024 Published online: October 03, 2024

Abstract

Aim: Deep Vein Thrombosis (DVT) is an acute onset disease. Warfarin and new oral anticoagulants (NOAC) can be used for treatment. Edoxaban is one of the NOACs that acts directly as a 'Factor Xa inhibitor'. The aim of our study was to investigate early treatment complications and efficacy in patients treated with warfarin and edoxaban.

Material and Methods: The results of a total of 100 patients who started drug treatment for DVT between September 2018 and March 2020 were retrospectively analysed. The patients included in the study were divided into two groups according to the type of anticoagulant used [Warfarin (n=50), Edoxaban (n=50)]. Patients' routine examinations and colour Doppler ultrasound (CDUSG) results at baseline and 1-month follow-up were compared with their bleeding status.

Results: Clinical status and CDUSG revealed acute DVT in 57 patients, subacute DVT in 32 patients, and chronic DVT in 11 patients. The recanalisation rate at 1 month was higher with edoxaban (80%) and lower with warfarin (62%) and this difference was statistically significant (p=0.008). The most common complication during follow-up was minor bleeding, which occurred in 24% and 18% of patients using Warfarin and Edoxaban, respectively. There was no mortality due to minor, major or cerebrovascular events in any of the patients.

Conclusion: In our study, we evaluated the early results of anticoagulant therapy in patients with DVT and found faster recanalization and fewer complications in the NOAC group in agreement with the literature. Further randomised, advanced and large-scale studies are needed to evaluate the efficacy of the drugs.

Keywords: Deep vein thrombosis, edoxaban, warfarin

INTRODUCTION

Venous thromboembolism (VTE) is a complex multifactorial disease involving deep vein thrombosis (DVT) and interactions between clinical risk factors and susceptibility to thrombosis, as summarised in Figure 1 [1]. Venous thromboembolism is a disease with high mortality (23% in 1 year) and morbidity, and 75% of cases are DVT patients [2]. The annual incidence of the first symptomatic DVT is between 50 and 100 per 100,000 [3].

Deep vein thrombosis is important because it is the major component of pulmonary embolism, the third most common cause of vascular death, and also because of the long duration of treatment [4,5]. In DVT, the most common complication is venous hypertension caused by increased permeability due to thrombus in the lower extremity veins, venous fibrosis and chronic inflammation [6].

CITATION
Guner A, Taban VB, Ceran MT, Dereli Y. Analysis of early results of edoxaban and warfarin in the treatment of deep vein thrombosis. Turk J Vasc Surg. 2024;33(3):127-31.

Corresponding Author: Abdullah Guner, Konya City Hospital, Department of Cardiovascular Surgery, Konya, Türkiye
Email: guner_426@hotmail.com

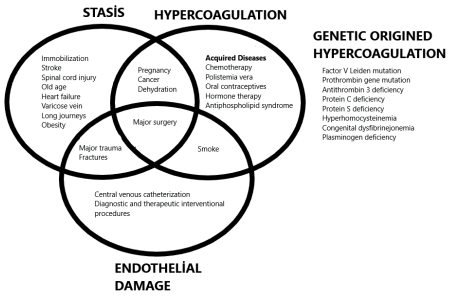

Figure 1. Venous thromboembolism etiology and risk factors [1]

Anticoagulation therapy is initiated to prevent venous thromboembolism and associated pulmonary embolism, chronic pulmonary hypertension and recurrent DVT. Until the last decade, the standard treatment for VTE was low molecular weight heparin (DMAH) and Warfarin treatment with an International Normalized Ratio (INR) value in the range of 2-3 in the first days, but due to the difficulties of this treatment and the inadequate rates of maintaining the INR at an effective level, New Oral Anticoagulant (NOAC) drugs emerged and started to be recommended by the guidelines because of their reliability in many trials [7,8].

The quality and efficacy of anticoagulant therapy in the treatment of DVT are recanalized flow in the early period, reduction in recurrent thrombosis, venous hypertension and pulmonary embolism and minimal incidence of minor or major bleeding [9]. In our study, we aimed to investigate the quality and effectiveness of treatment in patients treated with warfarin and edoxaban.

MATERIAL AND METHODS

Between September 2018 and March 2020, patients who were diagnosed with DVT by lower extremity colour Doppler ultrasound (CDUSG) and clinical examination, patients who started medical treatment, attended regular outpatient clinic check-ups, had complete archive documentation and adhered to medical treatment and, in patients receiving warfarin, those who achieved time in therapeutic range (TTR) and an effective INR range of 2-3 were included in the study. Patients who were pregnant and/or breastfeeding, patients younger than 18 years of age, patients with a history of thrombophilia, active bleeding, a glomerular filtration rate below 30 mL/min, DVT outside the femoral and popliteal regions on CDUSG, and patients with incomplete records were not included in the study. The results of a total of 100 patients included in the study were analyzed retrospectively. These patients were divided into two groups according to the type of anticoagulant used [Warfarin (n=50), Edoxaban (n=50)]. Detailed characteristics of the patients were obtained from file records and hospital software system. Minor (oral mucosal and gingival bleeding not requiring intervention, spontaneously resolved epistaxis and skin bleeding after trauma) and major [haemodynamically impaired, causing a fall in haemoglobin level of 2g/dl or more (if baseline is known) and bleeding in critical organs] bleeding and cerebrovascular events were determined from the medical history data. No other adverse events were identified. The study protocol was approved by the Necmettin Erbakan University Meram Medical Faculty Ethics Committee (date: 06.06.2020, no: 2020/2584). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Deep vein thrombosis time (acute, subacute, chronic) and provocation status were compared. Routine examinations and color Doppler ultrasonography results of the patients at the beginning of treatment and at 1-month follow-up and minor or major bleeding status were compared.

Statistical Methods

Statistical analyses were performed using SPSS 21.0 (IBM Inc, Chicago, IL, USA). Descriptive statistics of numerical and categorical data obtained in the study were analyzed and numerical valuables were expressed as median (IQR). Categorical variables were expressed as frequency and percentage. Kolmogorov-Smirnov test, histogram analyses and Skewness/Kurtosis data were used to evaluate the conformity of numerical variables to normal distribution. Since the numerical valuables did not show normal distribution characteristics, non-valuable tests were used as statistical methods. Mann-Whitney U test was used for two independent group comparisons and Kruskal-Wallis-H test was used for independent multiple group comparisons. The dependent Wilcoxon test was used to compare the values at different time points. Spearman's correlation analysis test was used for correlation between numerical values. Binary Logistic Regression analysis was used to determine the predictive factors. Chi-square test was used to analyze the relationship between binary or multiple categorical groups. Appropriate values were subjected to ROC analysis and diagnostic data were presented. The relationships between categorical groups and numerical values were summarized with boxplots. A type-I error rate of 5% was used as a base for the entire study and a value of $p<0.05$ was accepted as significant.

RESULTS

Of the 100 patients included in the study, 41 were female and 59 were male. The mean age was 58.40±12.40 years. The demographic data of the patients are shown in Table 1. In 10% of these patients, pulmonary embolism was found asymptomatically on examination in the emergency department. No genetic pattern or thrombotic event was found in 61% of the patients. Deep vein thrombosis was acute in 57%, subacute in 32% and chronic in 11% of the patients.

DOI: 10.9739/tjvs.2024.05.020

Table 1. Demographic data

		Frequency (n)
Age Group	**18-75 years**	93 (93%)
	>75 years	7 (7%)
Gender	**Woman**	59 (59%)
	Male	41 (41%)
Additional disease	**No**	81 (81%)
	HT	8 (8%)
	DM	6 (6%)
	Behcet's disease	3 (3%)
	COPD	2 (2%)

HT: hypertension DM: diabetus mellitus COPD: chronic obstructive pulmonary disease

When the provocation status was analysed, no provoking cause was found in 68% of the patients and provocation was found in only 32%. The provoked DVTs are shown in Table 2.

Table 2. Provocation distribution status

		Frequency (n)
Provocation causes	**COVID-19**	8 (25%)
	Hormone therapy	4 (12.5%)
	Immobilization	6 (18.75%)
	Advanced age (>80 years)	5 (15.6%)
	Malignancy	3 (9.4%)
	Obesity	2 (6.25%)
	Surgery	4 (12.5%)

In the CDUSG control performed at the first month, recanalized flow was detected in 71 patients; thrombus burden decreased in 67 patients, did not decrease in 7 patients and disappeared in 26 patients. The rate of recanalization at one month was 80% (40 patients) in the Edoxaban group and 60% (30 patients) in the warfarin group, showing a statistically significant difference (p=0.008). Thrombus burden did not decrease in 12% (6 patients) of the patients on Edoxaban and only 2% (1 patient) of the patients on Warfarin, and this difference was statistically significant (p=0.001) (Tables 3 and 4).

Table 3. Medication use and recanalisation status in the 1st month

Medicine		**1st month recanalized flow**	**1st month recanalized flow**	**X^2**	**p**
		None	**Available**		
Warfarin	**n**	19 (38%)	31 (62%)	9.599	**0.008**
Edoxaban	**n**	10 (20%)	40 (80%)		

X^2=chi-square test

Table 4. The relationship between medication and thrombus burden

Medicine		**1st month thrombus burden**	**1st month thrombus burden**	**X^2**	**p**
		No decrease	**Decreased/ disappeared**		
Warfarin	**n**	1 (2%)	49 (98%)	14.781	**0.001**
Edoxaban	**n**	6 (12%)	44 (88%)		

X^2=chi-square test

The D-Dimer value decreased significantly from a median of 147.4 ng/dl (95% CI, 23.7-345.3) in all patients before anticoagulant treatment to a median of 29.8 ng/dl (95% CI, 8.7-173.7) with treatment (p<0.001). No significant difference was observed between warfarin [median 144.2 ng/dl (95% CI, 34.8-310.6) to 31 ng/dl (95% CI, 22.3-169.5)] and edoxaban [158.2 ng/dl (95% CI, 26.3-377.1) to 29.8 ng/dl (95% CI, 21.7-133.4)] for D-dimer decline.

During anticoagulant treatment, 71 patients (71%) had no drug-related complications. 21 patients (21%) reported clinically insignificant 'minor bleeding' (oral mucosal and gingival bleeding not requiring intervention, spontaneously resolved epistaxis and skin bleeding after trauma were noted), which was the most common complication. Three patients (3%) were hospitalised for 'major bleeding' and no mortality was observed in any of these patients. A total of 5 patients (5%) had a cerebrovascular accident (CVA). The highest number of complications was observed in the Warfarin group with 32% and Table 5 summarises the complications in detail.

Table 5. Distribution of treatment complications according to drugs

		Warfarin (n: 50)	**Edoxaban (n: 50)**
Complication (1 month)	**No**	34 (68%)	38 (76%)
	Ischemic CVA	2 (4%)	2 (4%)
	Hemorrhagic CVA	1 (2%)	0 (0%)
	Minor bleeding	12 (24%)	9 (18%)
	Major bleeding	1 (2%)	1 (2%)

CVA: cerebrovascular accident

DISCUSSION

In a study by Silverstein et al. [10], the mean age at the onset of DVT was 61.7±20.4 years, whereas the mean age of patients in our study was 58.40±12.40 years. In general, patients over 75 years of age were less common in our population because hospitalised patients were excluded from the study and hospitalised patients were more likely to be treated as inpatients rather than outpatients. We believe this is the reason for the age difference.

A study by Ageno et al [11] showed the effect of comorbidities on DVT in a meta-analysis and reported that hypertension (HT) increased the frequency of DVT by an average of 1.51 times. In our study, the proportion of patients with DVT and HT was 8%. In a study by Piazza et al [12], the association between Diabetes Mellitus (DM) and DVT was investigated and the presence of DM was found in 19.2% of patients with DVT. In our study, DM was the second most common comorbidity with a prevalence of 6%. We believe that the reason for the difference between the two studies is that the study was conducted with an older age group (68.2 years) and the prevalence of DM increases with age. A study by Angelli et al [13] found that 8.8% of patients had PE at the time of DVT diagnosis. Similar to the literature, PE was observed in 10% of the patients in our study. According to the Turkish Thoracic Society Consensus Report, it was shown that the rate of detection of genetic pathology in individuals with VTE can vary between 10% and 50%, and in our study, a genetic association was found in 39%.

In their review of the GARFIELD-VTE study, Ageno et al [14] found that 59.2% of the 10,207 patients with DVT had 'unprovoked DVT', 30.7% had a temporary provoking cause and 10.1% had a permanent provoking factor. In our study, the rate of unprovoked DVT was 68% and the rate of provoked DVT was 32%, which is in line with the literature. In a study conducted during the pandemic period influenced by the Sars-Cov-19 virus, Joo Suh et al. [15] examined all patient groups with COVID-19 and showed that the incidence of DVT was 14.8%, indicating that it is an important cause of DVT, and in our study, COVID-19 was found to be the most common provoking cause with 26%.

The expected effect of anticoagulants drugs is early recanalisation of the venous lumen, which influences the prognosis of patients. The term recanalisation actually refers to partial openings that allow the passage of venous effluent rather than complete patency. Therefore, the efficacy of anticoagulants is closely related to the degree of recanalisation and a good anticoagulant becomes effective in the treatment of DVT by shortening the time to recanalisation. According to the reported figures, it has been observed that it takes up to 4 years for a patient with DVT to achieve complete recanalisation, the average recanalisation rate at the 1st month is 39%, and the quality of recanalisation is peripheral rather than central, although it varies [16,17]. In our study, the rate of completely and partially recanalised flow at month 1 was 69%. At the same time, the first-month recanalisation rate between the edoxaban group and warfarin groups was statistically more significant in the edoxaban group (80%) than in the warfarin group (62%) (p=0.008).

The main criteria for the selection of anticoagulants are drug safety and bleeding complications, and in HOKUSAI-VTE [18], a major bleeding rate of 1.4% was observed with edoxaban and lower bleeding rates were observed compared with warfarin treatment. In our study, the major bleeding rate was 2% in the edoxaban and warfarin groups, which is similar to the literature. Minor bleeding was better in the edoxaban group (Edoxaban 18%, Warfarin 24%).

CONCLUSION

New oral anticoagulant therapies have emerged as an alternative to warfarin and are associated with fewer anticoagulant therapy complications. In our study, we evaluated the early results of anticoagulant therapy in patients with DVT and found faster recanalisation and fewer complications in the NOAC group, which is consistent with the literature. Further randomised, larger trials are needed to assess the efficacy of the drugs.

Ethics Committee Approval: The study protocol was approved by the Necmettin Erbakan University Meram Medical Faculty Ethics Committee (date: 06.06.2020, no: 2020/2584). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: Informed consent was obtained from each patient before the procedure

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

Author Contributions: All authors contributed equally to the article.

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

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

REFERENCES

1. Yildirim MA, Isik M. Standard dose prophylaxis application and venous thromboembolism findings in patients who had bariatric surgery. Selcuk University Med J. 2021;37:245-50.
2. Tagalakis V, Patenaude V, Kahn SR, Suissa S. Incidence of and mortality from venous thromboembolism in a real-world population: the Q-VTE Study Cohort. Am J Med. 2013;126:832.e13-832.e8.32E21.
3. Kakkos SK, Gohel M, Baekgaard N, Bauersachs R, Bellmunt-Montoya S, Black SA, et al. Editor's Choice–European Society for Vascular Surgery (ESVS) 2021 clinical practice guidelines on the management of venous thrombosis. Eur J Vasc Endovasc Surg. 2021;61:9-82.
4. Doğan K, Selçuk T, Alkan A. An improved machine learning model for pulmonary embolism detection and segmentation. Preprints. Published online 28 April 2024. doi: 10.20944/preprints202404.1810.v1
5. Kearon C, Akl EA, Comerota AJ, Prandoni P, Bounameaux H, Goldhaber SZ, et al. Antithrombotic therapy for VTE disease: antithrombotic therapy and prevention of thrombosis: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2012;141:e419S-96S. Erratum in: Chest. 2012;142:1698-704.

6. Tick L, Kramer M, Rosendaal F, Faber W, Doggen C. Risk factors for post-thrombotic syndrome in patients with a first deep venous thrombosis. J Thromb Haemost. 2008;6:2075-81.

7. Becattini C, Agnelli G. Treatment of venous thromboembolism with new anticoagulant agents. J Am Coll Cardiol. 2016;67:1941-55.

8. Ortel TL, Neumann I, Ageno W, Beyth R, Clark NP, Cuker A, et al. American Society of Hematology 2020 guidelines for management of venous thromboembolism: treatment of deep vein thrombosis and pulmonary embolism. Blood advances. 2020;4:4693-738.

9. Kahn SR, Comerota AJ, Cushman M, Evans NS, Ginsberg JS, Goldenberg NA, et al. The postthrombotic syndrome: evidence-based prevention, diagnosis, and treatment strategies: a scientific statement from the American Heart Association. Circulation. 2014;130:1636-61. Erratum in: Circulation. 2015;131:e359.

10. Silverstein MD, Heit JA, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ. Trends in the incidence of deep vein thrombosis and pulmonary embolism: a 25-year population-based study. Arch Intern Med. 1998;158:585-93.

11. Ageno W, Becattini C, Brighton T, Selby R, Kamphuisen PW. Cardiovascular risk factors and venous thromboembolism: a meta-analysis. Circulation. 2008;117:93-102.

12. Piazza G, Goldhaber SZ, Kroll A, Goldberg RJ, Emery C, Spencer FA. Venous thromboembolism in patients with diabetes mellitus. Am J Med. 2012;125:709-16.

13. Agnelli G, Buller HR, Cohen A, Curto M, Gallus AS, Johnson M, et al. Oral apixaban for the treatment of acute venous thromboembolism. N Engl J Med. 2013;369:799-808.

14. Ageno W, Farjat A, Haas S, Weitz JI, Goldhaber SZ, Turpie AG, et al. Provoked versus unprovoked venous thromboembolism: findings from GARFIELD-VTE. Research and practice in thrombosis and haemostasis. 2021;5:326-41.

15. Suh YJ, Hong H, Ohana M, Bompard F, Revel M-P, Valle C, et al. Pulmonary embolism and deep vein thrombosis in COVID-19: a systematic review and meta-analysis. Radiology. 2021;298:E70-80.

16. Markel A, Meissner M, Manzo R, Bergelin R, Strandness Jr D. Deep venous thrombosis: rate of spontaneous lysis and thrombus extension. Int Angiol. 2003;22:376-82.

17. Puskas A, Balogh Z, Hadadi L, Imre M, Orban E, Kosa K, et al. Spontaneous recanalization in deep venous thrombosis: a prospective duplex ultrasound study. Int Angiol. 2007;26:53-63.

18. Investigators H-V. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. N Engl J Med. 2013;369:1406-15. Erratum in: N Engl J Med. 2014;370:390.