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Original Article

Novel oral anticoagulants' efficacy and safety in comparison to vitamin K antagonists and low molecular weight heparins

Yeni oral antikoagülanların etkinliklerinin ve güvenlik verilerinin vitamin K antagonistleri ve düşük molekül ağırlıklı heparinler ile karşılaştırılması

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ABSTRACT

Objective: The last standard treatment for venous thromboembolism (VTE) is oral anticoagulation with a vitamin K antagonist. Treatment with a vitamin K antagonist requires frequent monitoring of the international normalized ratio (INR), and these drugs have several disadvantages. Direct oral anticoagulants are alternative drugs to oral anti-vitamin K anticoagulants. With safer ranges, novel oral anticoagulants (NOACs) have been accepted in guidelines as drugs of choice. This study aimed to retrospectively examine the outcomes of three new-generation anticoagulant drugs in a patient group.
Methods: Two hundred eighteen adults were included in this retrospective cohort study. Patients are included in this study if they had been used any of these drugs in the past: Warfarin, low molecular weight heparin (LMWH), dabigatran, apixaban, and rivaroxaban. The study was conducted retrospectively for evaluating safety and effectiveness. Treatment charges for LMWH, warfarin, and NOAC were calculated based on info from the medical monitoring fee, approximate hospital transportation costs per INR measurement, and drug fees for 6 months.
Results: In comparison with warfarin (n: 1, 1.4%), the risk of embolism recurrence was found higher with apixaban (n: 6, 20%, RR: 14.4, OR: 17.75, 95% CI: 2.03-154.99, p=0.002) and rivaroxaban (n: 6, 19.4%, RR: 13.94, OR: 17.04, 95% CI: 1.95-148.57, p=0.003) in patient groups.
Conclusion: Compared to the literature, the rivaroxaban and apixaban groups had greater bleeding and recurrence risk in our study. This may be due to dietary habits and genetic factors.

Keywords: Factor Xa inhibitors, dabigatran etexilate, heparin, low molecular weight warfarin

ÖZ

Amaç: Venöz Trombombolizm(VTE)'de son standart tedavi, vitamin K antagonisti ile oral antikoagülasyondur. Bir K vitamini antagonisti ile tedavi, uluslararası normalleştirilmiş oranın (INR) sık sık izlenmesini gerektirir ve bu ilaçların çeşitli dezavantajları vardır. Doğrudan oral antikoagülanlar, oral anti-vitamin K antikoagülanlarına alternatif ilaçlardır. Daha güvenli aralıklarla yeni nesil oral antikoagülanlar (YOAK) kılavuzlarda kabul edilmiş ve tercih edilen ilaçlar haline gelmiştir. Bu çalışmada bir grup hastada üç yeni nesil antikoagülan ilacın sonuçlarını geriye dönük olarak incelemeyi amaçladık.
Yöntemler: Bu retrospektif kohort çalışmasına toplam 218 yetişkin dahil edildi. Çalışmamızın örneklemini tedavilerinde warfarin, düşük molekül ağırlıklı heparin (DMAH), dabigatran, apixaban ve rivaroxaban'dan herhangi birini kullanan hastalar (n=218) oluşturmuştur. Çalışmada güvenlik ve etkinlik verileri geriye dönük tarandı. DMAH, warfarin ve YOAK için tedavi maliyetleri, tıbbi izlem için harcanan ücretler, INR ölçümleri için hastaneye ulaşım ücretleri ve altı aylık ilaç ücretleri hesaplanarak belirlendi.

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Bulgular: Warfarin ile karşılaştırıldığında (n: 1, %1,4) emboli nüksü riski apixaban grubunda daha yüksek bulundu (n: 6, %20, RR: 14,4, OR: 17,75, %95 GA: 2,03-154,99, p=0,002) ve rivaroxaban (n: 6, %19.4, RR: 13.94, OR: 17.04, %95 GA: 1.95-148.57, p=0.003) hasta grubunda da daha yüksekti.
Sonuç: Çalışmamızda literatürden farklı olarak rivaroksaban ve apiksaban gruplarında daha fazla kanama ve emboli nüksü görüldü. Bunun nedeni beslenme alışkanlıkları ve genetik faktörler olabilir.

Anahtar kelimeler: Faktör Xa inhibitörleri, dabigatran etexilate, heparin, düşük molekül ağırlıklı, warfarin

INTRODUCTION

Venous thromboembolism (VTE) affects 1 to 2 individuals per 1000 people each year, and it is the third leading cause of vascular death after stroke and myocardial infarction (1,2). Major surgery, major trauma, previous VTE, obesity, spinal cord injury, growing old, cardiac/respiratory failure, malignancy, prolonged immobility, estrogens, central venous lines, inherited/ acquired hematological disorders are risk factors for VTE (3). People who are not hospitalized or recovering from a severe illness comprises 25-50% of VTE cases (4,5). Rapid-acting parenteral anticoagulation for 5 to 7 days initially is the standard treatment, followed by at least 3 months with a vitamin K antagonist (VKA) (6). Treatment with a VKA necessitates frequent monitoring of the international normalized ratio (INR), and there have been numerous reports of VKA interactions with foods and other medications (6,7). Therefore, these drugs have a number of disadvantages. These include frequent dose and coagulation status adjustments, and multiple drug-drug interaction and the need for diet monitoring (8).

Warfarin dissolves blood clots and prevents occuring new clot formation by inhibiting the synthesis of specific clotting proteins that rely on vitamin K. The dose of warfarin is taken once daily by mouth and varies depending on genetic factors, the reason of therapy, and dietary habits. Warfarin requires periodic laboratory monitoring and dose adjustment to keep the blood level of international normalized ratio (INR) within the target range. Therefore, dose required for each patient vary. Patients whose blood levels are below the target range are more likely to clot. The risk of bleeding increases as blood levels rise above the target range. All anticoagulants, including warfarin, increase the risk of hemorrhage. In such cases, vitamin K or other blood products may be used to replace the warfarin-affected clotting factors (9).

Direct oral anticoagulants are alternative remedies to oral anti-vitamin K anticoagulants. Nevertheless, the interindividual variability of effects of these remedies is important factor and may lead to hemorrhagic or thromboembolic events (9).

Because of the useful issues with other oral anticoagulants except VKA, new generation anticoagulants quickly found compherensive area of use in the medicine. Anticoagulants such as dabigatran, rivaroxaban, and apixaban with safer therapeutic intervals have been accepted in clinical guidelines and have taken their place as favored drugs (10). In this study, we aimed to retrospectively investigate the results of three new-generation anticoagulant drugs in a group of patients.

MATERIALS AND METHODS

Study Design

A total of 218 adults were included in this retrospective cohort study. The sample of the study consisted of all patients (n=218) who applied to our university hospital and diagnosed with VTE between 01.12.2015 and 31.03.2018 and used any of the drugs: warfarin, lmwh, dabigatran, apixaban and rivaroxaban in their treatment and study were conducted retrospectively for safety, cost effectiveness and clinically effectiveness.

Each patient's demographic, clinic, and imaging datas were collected. The information for the study obtained from the hospital's digital patient files and archive. Ultrasonography (USG), computed tomography (CT), or magnetic resonance (MR)

imaging were used to diagnose DVT in cases. Acute thrombosis of the lower extremity's deep proximal or distal veins was identified. Patients who were diagnosed with acute VTE in their data files, were evaluated by the consultation team and started anticoagulation in the emergency department or cardiovascular surgery service and were followed up were included in the study. We used the fees corresponding to the SUT codes determined by the Ministry of Health of the Republic of Turkiye for calculating the costs (11).

Exclusion criteria contained symptomatic pulmonary embolism (PE), alanine aminotransferase (ALT) ≥3 times the upper limit of normal, calculated creatinine clearance below 30ml/min, bacterial endocarditis, insertion of a caval filter, or use of a fibrinolytic agent to treat the recent attack of DVT, indications for VKAs other than DVT, thrombectomy, life-expectancy <6 months, active hemorrhage or high risk for hemorrhage contraindicating treatment with fondaparinux, LMWH or VKA, breastfeeding, pregnancy, patients with uncontrolled hypertension, and any other contraindication listed in the local labeling of enoxaparin, fondaparinux, warfarin, tinzaparin, phenprocoumon or acenocoumarol. Patients younger than 18 years, and patients with missing data were excluded from the study.

Patient recruitment and treatment

The choice of anticoagulant in a decision-making process shared with the patient, is determined by taking into consideration of published guidelines, results of clinical trials, route of management, and details from the package insert that include adjustment according to renal function, drug interactions etc.

LMWH 1.0 mg/kg of body weight, once or twice daily for the first 8 days; simultaneously, patients were initiated with a once-daily dose. The VKA drug is approximately determined in the model with an average dose of 4.5 mg for the planned 3, 6, or 12 months of treatment. Rivaroxaban 15 mg, twice daily for the first 21 days; followed by 20 mg once daily for the planned 3, 6, or 12 months of treatment. After 5 to 10 days of parenteral anticoagulation, edoxaban is administered. Dosing is usually 30 or 60 mg orally once a day (12). Apixaban; 10 mg twice daily for seven days, followed by 5 mg twice daily (13). Dabigatran; 150 mg orally twice daily after 5 to 10 days (9).

Costs

Treatment charges for LMWH, warfarin and NOAH were based on info from the medical monitoring fee, approximate hospital transportation costs per INR measurement, and drug fees for 6 months. We did not include treatment fees for complications in the costs. Medicine costs were calculated by combining data on daily doses and the associated daily reimbursed medicine cost. The number of days that patients were treated with LMWH and VKA were also used to determine this group's acute treatment drug cost. As a result, the drug acquisition costs were calculated using the Turkish Medicines and Medical Devices (TITCK) recent price bulletin (December 2021).

Statistical Analysis

SPSS version 23 (SPSS, Statistical Package for Social Sciences, IBM Inc., Armonk, NY, USA) package software was used to analyze the data obtained in this study. The frequency and percentage of categorical variables were provided. The Shapiro-Wilk test was used to determine the normalcy of the continuous variables. Mann-Whitney U test was used to compare variables between two groups, and the Kruskal-Wallis test (Post Hoc: Dunn-Bonferroni test) was used to compare variables between three groups. The Pearson's Chi-square test or Fisher's Exact Test examined the relationship between two categorical variables. Spearman's correlation analysis examined the relationship between two continuous variables. The continuous variables were represented by the median and interquartile range [IQR]. Values of p 0.05 were considered statistically significant.

Ethics Consideration

University hospital local ethics committee (Karabuk University Non-Interventional Clinical

Research Ethics Committee, date: 28.03.2018, issue number: 4/16) approved the study protocol. The research was carried out in accordance with the Helsinki Declaration. Due to the study's retrospective design, informed consent was waived.

RESULTS

A total of 218 VTE patients were included in the study. The youngest patient in the study was 20 years old, and the oldest patient was 88 years old. The median age of 218 patients was 58 (44.7-71), 116 (53.2%) were male. The disease relapsed in 15 (6.9%) patients during the treatment. Recurrence was similar in terms of age and gender (Z=-0.740, p=0.459; χ^2=1.129, p=0.288, respectively). Recurrence was observed in 5 (7.6%) of 66 patients with genetic predisposition and in 10 (6.6%) of 152 patients without a genetic predisposition. No significant difference was found in the number of recurrences according to genetic predisposition (p=0.776). Similarly, there was no significant difference in the number of relapses in 6 (7.2%) of 83 smokers and 9 (6.7%) of 135 non-smokers (χ^2=0.025, p=0.873) (Table 1).

Efficacy outcomes

In comparisons with warfarin (n: 1, 1.4%), the risk of recurrence was found higher with apixaban (n: 6, 20%, RR: 14.4, OR: 17.75, 95% CI: 2.03-154.99, p=0.002) and rivaroxaban (n: 6, 19.4%, RR: 13.94, OR: 17.04, 95% CI: 1.95-148.57, p=0.003) in patient groups (Table 2).

In comparison between Dabigatran and apixaban, rivaroxaban and edoxaban, apixaban with rivaroxaban and edoxaban the risk of recurrence was found to be similar (respectively; p=0.103, p=0.104, p=1.000, p=1.000, p=0.103). Table 3 shows the comparison of new-generation oral anticoagulants among themselves.

Safety outcomes

When the developing side effects were examined, the risk of ecchymosis in dabigatran (n: 1, 3.3%, RR: 0.08, OR: 0.05 (0.01-0.4), p=0.001), apixaban (n: 2, 6.7%, RR: 0.16, OR: 0.10 (0.02-0.50), p=0.003), rivaroxaban (n: 1, 3.2%, RR: 0.08, OR: 0.04 (0.01-0.39), p<0.001) and edoxaban (n: 3, 10.3%, RR: 0.24, OR: 0.16 (0.04-0.65), p=0.012) groups were found to be significantly lower than LMWH (n: 11, 42.3%) group. In the patient group receiving rivaroxaban, anemia (n: 9, 29%, RR: 2.61, OR: 3.27 (1.12-9.53), p=0.040), epistaxis (n: 5, 16.1%, RR: 5.81, OR: 6.73 (1.23) -36.86), p=0.025), and risk of major bleeding (n: 9, 29%, RR: 2.61, OR: 3.27 (1.12-9.53), p=0.040) were higher than warfarin group (respectively, n: 8, 11.1%, n: 2, 2.8%, n: 8, 11.1%) (Table 2).

Table 1. The number of recurrences of the disease according to the general characteristics of the patients.

		Recurrences	
	Total	**No**	**Yes**
Age, year, med (Q1-Q3, min-max)	58 (44.7-71, 20-88)	58 (44-71, 20-80)	64 (50-73, 24-82)
Gender-F/M, n (%)	102 (46.8) / 116 (53.2)	93 (91.2) / 110 (94.8)	9 (8.8) / 6 (5.2)
CVD-No/Yes, n (%)	208 (95.4) / 10 (4.6)	193 (92.8) / 10 (100)	15 (7.2) / 0 (0)
Gonarthrosis-No/Yes, n (%)	206 (94.5) / 12 (5.5)	191 (92.7) / 12 (100)	15 (7.3) / 0 (0)
HT-No/Yes, n (%)	188 (86.2) / 30 (13.8)	175 (93.1) / 28 (93.3)	13 (6.9) / 2 (6.7)
DM-No/Yes, n (%)	205 (94.4) / 13 (5.6)	190 (92.7) / 13 (100)	15 (7.3) / 0 (0)
COPD-No/Yes, n (%)	197 (90.4) / 21 (9.6)	184 (93.4) / 19 (90.5)	13 (6.6) / 2 (9.5)
Pregnancy[a]-No/Yes, n (%)	98 (96.08) / 4 (3.92)	89 (90.8) / 4 (100)	9 (9.2) / 0 (0)
Alzheimer-No/Yes, n (%)	214 (98.2) / 4 (1.8)	199 (93) / 4 (100)	15 (7) / 0 (0)
Malignancy-No/Yes, n (%)	203 (93.1) / 15 (6.9)	188 (92.6) / 15 (100)	15 (7.4) / 0 (0)
AF-No/Yes, n (%)	196 (89.9) / 22 (10.1)	183 (93.4) / 20 (90.9)	13 (6.6) / 2 (9.1)
Genetical Factors-No/Yes, n (%)	152 (69.7) / 66 (30.3)	142 (93.4) / 61 (92.4)	10 (6.6) / 5 (7.6)
Smoking-No/Yes, n (%)	135 (61.9) / 83 (38.1)	126 (93.3) / 77 (92.8)	9 (6.7) / 6 (7.2)

F/M: female/male, CVD: cerebrovascular disease, HT: hypertension, DM: diabetes mellitus, COPD: chronic obstructive pulmonary disease, AF: atrial fibrillation.

Table 2. Comparison of dabigatran, apixaban, rivaroxaban and edoxaban drugs according to lmwh and warfarin.

	LMWH n=26	Warfarin n=72	Dabigatran n=30	Apixaban n=30	Rivaroxaban n=31	Edoxaban n=29
Recurrence, n (%)	0 (0)	1 (1.4)	1 (3.3)	6 (20)	6 (19.4)	1 (3.4)
RR_2, OR_2 (95% CI)	-	-	2.40, 2.45, (0.15-40.47)	**14.4, 17.75, (2.03-154.99)***	**13.94, 17.04, (1.95-148.57)***	2.48, 2.54 (0.15-41.95)
Common advers effects, n (%)	14 (53.8)	20 (27.8)	8 (26.7)	12 (40)	13 (41.9)	13 (44.8)
RR_1, OR_1 (95% CI)	-	-	0.5, 0.31, (0.10-0.95)	0.74, 0.57, (0.2-1.65)	0.78, 0.62, (0.22-1.77)	0.83, 0.70 (0.24-2.02)
RR_2, OR_2 (95% CI)	-	-	0.96, 0.95, (0.36-2.47)	1.44, 1.73, (0.71-4.24)	1.51, 1.88, (0.78-4.53)	1.61, 2.11 (0.86-5.17)
GIS bleeding, n (%)	0 (0)	2 (2.8)	2 (6.7)	1 (3.3)	2 (6.5)	2 (6.9)
RR_2, OR_2 (95% CI)	-	-	2.40, 2.50, (0.34-18.63)	1.20, 1.21, (0.11-13.84)	2.32, 2.41 (0.32-17.96)	2.48, 2.59 (0.35-19.34)
Anemia, n (%)	5 (19.2)	8 (11.1)	4 (13.3)	6 (20)	9 (29)	4 (13.8)
RR_1, OR_1 (95% CI)	-	-	0.69, 0.65, (0.15-2.71)	1.04, 1.05, (0.28-3.94)	1.51, 1.72 (0.49-5.97)	0.72, 0.67 (0.16-2.83)
RR_2, OR_2 (95% CI)	-	-	1.2, 1.23, (0.34-4.44)	1.8, 2, (0.63-6.37)	**2.61, 3.27 (1.12-9.53)***	1.24, 1.28 (0.35-4.63)
Subconjunctival hemorrhage, n (%), n (%)	3 (11.5)	1 (1.4)	0 (0)	1 (3.3)	0 (0)	2 (6.9)
RR_1, OR_1 (95% CI)			-	0.29, 0.26, (0.03-2.71)	-	0.60, 0.57 (0.09-0.3.70)
RR_2, OR_2 (95% CI)			-	2.4, 2.45, (0.15-40.47)	-	4.97, 5.26 (0.46-60.40)
Hematuria, n (%)	4 (15.4)	3 (4.2)	1 (3.3)	1 (3.3)	4 (12.9)	2 (6.9)
RR_1, OR_1 (95% CI)	-	-	0.22, 0.19, (0.02-1.82)	0.22, 0.19, (0.02-1.82)	0.84, 0.81 (0.18-3.64)	0.45, 0.41 (0.07-2.44)
RR_2, OR_2 (95% CI)	-	-	0.8, 0.79, (0.08-7.95)	0.8, 0.79, (0.08-7.95)	3.10, 3.41 (0.71-16.24)	1.66, 1.70 (0.27-10.77)
Pruritis, n (%)	3 (11.5)	4 (5.6)	1 (3.3)	1 (3.3)	1 (3.2)	1 (3.4)
RR_1, OR_1 (95% CI)	-	-	0.29, 0.26, (0.03-2.71)	0.29, 0.26, (0.03-2.71)	0.28, 0.26 (0.03-2.62)	0.30, 0.27 (0.03-2.81)
RR_2, OR_2 (95% CI)	-	-	0.6, 0.59, (0.06-5.47)	0.6, 0.59, (0.06-5.47)	0.58, 0.57 (0.06-5.29)	0.62, 0.61 (0.06-5.67)
Ecchymosis, n (%)	11 (42.3)	5 (6.9)	1 (3.3)	2 (6.7)	1 (3.2)	3 (10.3)
RR_1, OR_1 (95% CI)	-	-	**0.08, 0.05, (0.01-0.4)****	**0.16, 0.1, (0.02-0.5)***	**0.08, 0.04 (0.01-0.39)****	**0.24, 0.16 (0.04-0.65)***
RR_2, OR_2 (95% CI)	-	-	0.48, 0.46, (0.05-4.13)	0.96, 0.96, (0.18-5.23)	0.46, 0.45 (0.05-3.99)	1.49, 1.54 (0.34-6.94)
Epistaxis, n (%), n (%)	2 (7.7)	2 (2.8)	0 (0)	3 (10)	5 (16.1)	1 (3.4)
RR_1, OR_1 (95% CI)	-	-	-	1.3, 1.33, (0.21-8.67)	2.10, 2.31 (0.41-13.03)	0.45, 0.43 (0.04-5.02)
RR_2, OR_2 (95% CI)	-	-	-	3.6, 3.89, (0.62-24.57)	**5.81, 6.73 (1.23-36.86)***	1.24, 1.25 (0.11-14.34)
Genital bleeding, n (%)	2 (7.7)	6 (8.3)	3 (10)	4 (13.3)	4 (12.9)	2 (6.9)
RR_1, OR_1 (95% CI)	-	-	1.3, 1.33, (0.21-8.67)	1.73, 1.85, (0.31-11.01)	1.68, 1.78 (0.30-10.59)	0.90, 0.89 (0.12-6.81)
RR_2, OR_2 (95% CI)	-	-	1.2, 1.22, (0.28-5.24)	1.6, 1.69, (0.44-6.49)	1.55, 1.63 (0.43-6.24)	0.83, 0.81 (0.15-4.29)
Majör bleeding, n (%)	4 (15.4)	8 (11.1)	4 (13.3)	8 (26.7)	9 (29)	5 (17.2)
RR_1, OR_1 (95% CI)	-	-	0.87, 0.85, (0.19-3.78)	1.73, 2, (0.52-7.62)	1.89, 2.25 (0.60-8.40)	1.12, 1.15 (0.27-4.82)
RR_2, OR_2 (95% CI)	-	-	1.2, 1.23, (0.34-4.44)	2.4, 2.91, (0.97-8.68)	**2.61, 3.27 (1.12-9.53)***	1.55, 1.67 (0.50-5.60)
Increase menstrual bleeding, n (%)	2/12 (16.7)	2/32 (6.3)	1/11 (9.1)	1/16 (6.3)	1/18 (5.6)	1/13 (7.7)
RR_1, OR_1 (95% CI)	-	-	0.04, 0.92, (0.67-1.26)	0.38, 0.33, (0.03-4.19)	0.33, 0.29, (0.02-3.67)	0.46, 0.42 (0.03-5.30)
RR_2, OR_2 (95% CI)	-	-	1.45, 1.5, (0.12-18.36)	1, 1, (0.08-11.93)	0.89, 0.88, (0.07-10.46)	1.23, 1.25 (0.10-15.11)

RR1, OR1: Relative risk and odds ratio for comparison of Dabigatran, Apixaban, Rivaroxaban and Edoxaban according to LMWH (Ref.),
RR2, OR2: Relative risk and odds ratio for comparison of Dabigatran, Apixaban, Rivaroxaban and Edoxaban drugs relative to Warfarin (Ref.).
**: p<0.05, **: p<0.001, Fisher Exact test.*
[a]: Analysis was performed only on female patients

Table 3. Relative risk and odds ratios for comparison of dabigatran, rivaroxaban, apixaban and edoxaban drugs.

	Dabigatran n=30	Apixaban n=30	Rivaroxaban n=31	Edoxaban n=29
Recurrences, n (%)	1 (3.3)	6 (20)	6 (19.4)	1 (3.4)
RR_1, OR_1 (95% CI)	-	6, 7.25, (0.82-64.46)	5.81, 6.96, (0.78-61.79)	1.03, 1.04, (0.06-17.38)
RR_2, OR_2 (95% CI)	-	-	0.97, 0.96, (0.27-3.39)	0.17, 0.14, (0.02-1.27)
RR_3, OR_3 (95% CI)	-	-	-	0.18, 0.15, (0.02-1.32)
Common advers effects, n (%)	8 (26.7)	12 (40)	13 (41.9)	13 (44.8)
RR_1, OR_1 (95% CI)	-	1.5, 1.83, (0.62-5.45)	1.57, 1.99, (0.68-5.84)	1.68, 2.23, (0.75-6.65)
RR_2, OR_2 (95% CI)	-	-	1.05, 1.08, (0.39-3.01)	1.12, 1.22, (0.43-3.43)
RR_3, OR_3 (95% CI)	-	-	-	1.07, 1.13, (0.4-3.13)
GI bleeding, n (%)	2 (6.7)	1 (3.3)	2 (6.5)	2 (6.9)
RR_1, OR_1 (95% CI)	-	0.5, 0.48, (0.04-5.63)	0.97, 0.97, (0.13-7.33)	1.03, 1.04, (0.14-7.90)
RR_2, OR_2 (95% CI)	-	-	1.94, 2.0, (0.17-23.29)	2.07, 2.15, (0.18-25.07)
RR_3, OR_3 (95% CI)	-	-	-	1.07, 1.07, (0.14-8.17)
Anemia, n (%)	4 (13.3)	6 (20)	9 (29)	4 (13.8)
RR_1, OR_1 (95% CI)	-	1.5, 1.63, (0.41-6.47)	2.18, 2.66, (0.72-9.83)	1.03, 1.04, (0.23-4.62)
RR_2, OR_2 (95% CI)	-	-	1.45, 1.64, (0.50-5.35)	0.69, 0.64, (0.16-2.55)
RR_3, OR_3 (95% CI)	-	-	-	0.48, 0.39, (0.11-1.45)
Subconjunctival hemorrhage, n (%)	0 (0)	1 (3.3)	0 (0)	2 (6.9)
RR_2, OR_2 (95% CI)	-	-	-	2.07, 2.15, (0.18-25.07)
Hematuria, n (%)	1 (3.3)	1 (3.3)	4 (12.9)	2 (6.9)
RR_1, OR_1 (95% CI)	-	1, 1, (0.06-16.76)	3.87, 4.3, (0.45-40.89)	2.07, 2.15, (0.18-25.07)
RR_2, OR_2 (95% CI)	-	-	3.87, 4.3, (0.45-40.89)	2.07, 2.15, (0.18-25.07)
RR_3, OR_3 (95% CI)	-	-	-	0.53, 0.5, (0.08-2.96)
Pruritis, n (%)	1 (3.3)	1 (3.3)	1 (3.2)	1 (3.4)
RR_1, OR_1 (95% CI)	-	1, 1, (0.06-16.76)	0.97, 0.97, (0.06-16.19)	1.03, 1.04, (0.06-17.38)
RR_2, OR_2 (95% CI)	-	-	0.97, 0.97, (0.06-16.19)	1.03, 1.04, (0.06-17.38)
RR_3, OR_3 (95% CI)	-	-	-	1.07, 1.07, (0.06-17.96)
Ecchymosis, n (%)	1 (3.3)	2 (6.7)	1 (3.2)	3 (10.3)
RR_1, OR_1 (95% CI)	-	2, 2.07, (0.18-24.15)	0.97, 0.97, (0.06-16.19)	3.1, 3.35, (0.33-34.19)
RR_2, OR_2 (95% CI)	-	-	0.48, 0.47, (0.04-5.44)	1.55, 1.62, (0.25-10.45)
RR_3, OR_3 (95% CI)	-	-	-	3.21, 3.46, (0.34-35.34)
Epistaxis, n (%)	0 (0)	3 (10)	5 (16.1)	1 (3.4)
RR_2, OR_2 (95% CI)	-	-	1.61, 1.73, (0.38-7.99)	0.34, 0.32, (0.03-3.28)
RR_3, OR_3 (95% CI)	-	-	-	0.21, 0.19, (0.02-1.7)
Genital bleeding, n (%)	3 (10)	4 (13.3)	4 (12.9)	2 (6.9)
RR_1, OR_1 (95% CI)	-	1.33, 1.38, (0.28-6.8)	1.29, 1.33, (0.27-6.53)	0.69, 0.67, (0.1-4.31)
RR_2, OR_2 (95% CI)	-	-	0.97, 0.96, (0.22-4.26)	0.52, 0.48, (0.08-2.86)
RR_3, OR_3 (95% CI)	-	-	-	0.53, 0.5, (0.08-2.96)
Majör bleeding, n (%)	4 (13.3)	8 (26.7)	9 (29)	5 (17.2)
RR_1, OR_1 (95% CI)	-	2, 2.36, (0.63-8.92)	2.18, 2.66, (0.72-9.83)	1.29, 1.35, (0.33-5.64)
RR_2, OR_2 (95% CI)	-	-	1.09, 1.13, (0.37-3.45)	0.65, 0.57, (0.16-2.02)
RR_3, OR_3 (95% CI)	-	-	-	0.59, 0.51, (0.15-1.75)
Increase menstrual bleeding[a], n (%)	1/11 (9.1)	1/16 (6.3)	1/18 (5.6)	1/13 (7.7)
RR_1, OR_1 (95% CI)	-	0.69, 0.67, (0.04-11.94)	0.61, 0.59, (0.03-10.48)	0.85, 0.83, (0.05-15.09)
RR_2, OR_2 (95% CI)	-	-	0.89, 0.88, (0.05-15.37)	1.23, 1.25, (0.07-22.13)
RR_3, OR_3 (95% CI)	-	-	-	1.38, 1.42, (0.08-24.95)

RR1, OR1: Relative risk and odds ratio for comparison of Rivaroxaban, Apixaban and Edoxaban drugs relative to Dabigatran (Ref.),
RR2, OR2: Relative risk and odds ratio for comparison of Rivaroxaban and Edoxaban drugs relative to Apixaban (Ref.)
RR3, OR3: Relative risk and odds ratio of Edoxaban drugs compared to Rivoroxsaban (Ref.).
**: $p<0.05$, **: $p<0.001$, Fisher Exact test.*
[a]: Analysis was performed only on female patients

DISCUSSION

Other studies have compared the cost-effectiveness of rivaroxaban in different clinical procedures. Rivaroxaban was shown to be a cost-effective alternative to warfarin in preventing stroke in patients in one study (14). When rivaroxaban and apixaban were compared to warfarin in this study, the recurrence rate was higher in rivaroxaban and apixaban. Because the new generation drugs are more expensive, apixaban and rivaroxaban cannot be considered cost-effective. Only ecchymotic lesions were significantly lower in the rivaroxaban group. In another study by Seaman et al.[15] gastrointestinal (GI) bleeding was more common in the warfarin group than in the rivaroxaban group. Interestingly, we found that the incidence of GI bleeding with rivaroxaban compared with warfarin was 6.5% vs. 2.8%, respectively; however, there was no difference in the rate of non-major bleeding between the two treatment groups. Studies making comparison between LMWH and rivaroxaban are available in the literature. Rivaroxaban and enoxaparin had no difference in terms of complications and DVT formation in a study of patients undergoing ligament arthroplasty (13). In another study, significantly less bleeding was observed in patients using rivaroxaban (16). Similar to the literature, no significant difference was observed in general side effects.

Weycker et al.[13] showed that apixaban had significantly lower bleeding risk than warfarin. There was no difference between the groups according to bleeding risk in our study, but the risk of DVT recurrence was higher in the apixaban group.

Schulman et al.[9] showed that dabigatran was superior to warfarin in developing DVT and bleeding complications. However, he states that the side effects resulting in discontinuation of the drug are higher in dabigatran. Another study on dabigatran was associated with lower stroke and systemic embolism rates but similar major bleeding rates compared to warfarin (17). In our results, dabigatran was similar to warfarin and LMWH in terms of side effects and DVT recurrence.

In the large, double-blind study of Hokusai[12] involving patients with DVT, heparin followed by once-daily oral edoxaban was found more effective and superior in bleeding than warfarin therapy. However, there was no recurrence in the LMWH group in our population. The reason for this may be the small number of patients in the LMWH group. In addition, there was no difference between the edoxaban and warfarin groups in terms of recurrence risk. However, less ecchymosis was observed in the edoxaban group.

Our results are interestingly inconsistent with those shown in previously completed financial evaluation studies with NOACs versus VKA and LMWH for DVT treatment. While other studies have shown that NOACs are cost-effective anticoagulation alternatives to VKA and LMWH in DVT treatment, our study has different results for rivaroxaban and apixaban group (18-20). The reason for this may be the regional circumstances and genetic differentiation. Conducting studies in different races and societies with a large patient samples may resolve the question marks. It is thought that more studies are needed to clear these doubts. In this study, an economic analysis was done to compare the effectiveness and cost-effectiveness of NOACs, enoxaparin, and dose-adjusted VKAs for treating DVT in the Western Black Sea region of Turkey.

In conclusion; the high cost of NOACs, when considered together with these results, causes the government to be paid, which is an economic burden. Although transportation charges were added for the warfarin user's hospital visit, it offered less cost.

Ethics Committee Approval: The study protocol was approved by the Karabuk University Non-Interventional Clinical Research Ethics Committee (28.03.2018 / 4/16).

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