Effect of Direct-acting Oral Anticoagulants and Warfarin on Hospital Outcomes in Upper Gastrointestinal Bleeding

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ABSTRACT

Objective: To evaluate the comparison of direct-acting oral anticoagulants (DOACs) and warfarin for their effects on major bleeding and hospital outcomes in patients with acute nonvariceal upper gastrointestinal bleeding (NVUGIB).

Study Design: An observational study.

Place and Duration of Study: Tekirdag Namik Kemal University Hospital, Hitit University Erol Olçok Education and Research Hospital, between January and December 2021.

Methodology: Adult patients prescribed warfarin and DOACs were followed up for one year. Their length of hospital stay, need for intensive care unit admission, need for red blood cell transfusion, and major bleeding rates were compared.

Results: Thirty-two patients (61.5%) were user of DOACs (DOAC group), and 20 patients (38.5%) were users of warfarin (warfarin group). No statistically significant difference was determined between patients in warfarin group and DOAC group for the number of packed red blood cells transfused [median 3 (0-6) units, 3 (0-10) units, p=0.229, respectively], length of hospital stay [median 5 days (3-10), and 4.5 days (2-20), p=0.739, respectively], rate of intensive care unit admission [(n=9, 45%; and n=10 (31%), p=0.623, respectively] and the occurrence of major bleeding events (warfarin-70%; DOACs-78%; p=0.529).

Conclusion: Major bleeding episodes and hospital outcomes of acute NVUGIB were similar between patients receiving warfarin and DOACs.

Key Words: *Direct-acting oral anticoagulants, Warfarin, Gastrointestinal bleeding, Outcome, Mortality.*

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INTRODUCTION

Upper gastrointestinal bleeding is a gastrointestinal disorder caused by oesophageal, gastric, and duodenal lesions and most often requires hospitalisation.[1,2] Despite the development of advanced endoscopic treatments over the last 20-50 years, the mortality rate associated with nonvariceal upper gastrointestinal bleeding (NVUGIB), has not changed.[3-5] While it is assumed that the incidence of NVUGIB decreases with the use of proton pump inhibitors and the administration of effective acid suppression therapy, in contrast, in recent years, an increase in the occurrence of NVUGIB has been observed with the use of oral anticoagulants and nonsteroidal anti-inflammatory agents.[2]

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Gastrointestinal bleeding (GIB) is a major complication of oral anticoagulant treatment.[6] Warfarin, an oral anticoagulant used as a vitamin K antagonist, is preferred in cases of venous thrombosis, pulmonary thromboembolism, atrial fibrillation, cerebrovascular disease, and valvular heart disease. The most significant side effect of warfarin, which has been used for many years, is severe life-threatening GIB.[7,8] Direct-acting oral anticoagulants (DOACs), including apixaban, dabigatran, edoxaban, and rivaroxaban, have been developed as alternatives to warfarin. When compared to warfarin, DOACs have the advantages of not interacting with other drugs and food and no need for monitoring.[9] DOACs are preferred based on their fixed-dose regimen with no need for laboratory monitoring and fewer drug interactions. GIB is the primary complication associated with the use of DOACs.[10] The effects of warfarin and DOACs on the severity of GIB and hospital outcomes are controversial.

The aim of this study was to compare the outcome of NVUGIB in patients taking warfarin and DOACs (dabigatran, rivaroxaban, apixaban, and edoxaban). The authors investigated the effects of warfarin and DOACs on acute NVUGIB based on patients' Charlson comorbidity index scores, length of hospital stay, need for intensive care unit admission, need for red blood cell (RBC) transfusion, and major bleeding rate.

METHODOLOGY

This study was a multicentre study conducted prospectively at two Turkish institutions, namely Tekirdag Namık Kemal University Hospital and Hitit University Erol Olçok Education and Research Hospital. Patients included in this study were followed up at the gastroenterology clinic between January 1 and December 31, 2021, and evaluated for acute NVUGIB. The study protocol (2020.241.11.01) was approved by the Ethics Committee at Tekirdağ Namık Kemal University. The study protocol conformed to the guidelines of the Declaration of Helsinki. Written informed consent were obtained from each patient. Among the follow-up patients, those who were aged 18 years or over, did not have a previous bleeding event and received anticoagulation treatment with warfarin or DOACs were chosen. Patients who were diagnosed with oesophageal, gastric or duodenal cancer and gastric and/or oesophageal varices and patients younger than 18 years of age were excluded from the study. Patients treated with new antiplatelet agents, antithrombotics, histamine type 2 receptor antagonists/blockers or proton pump inhibitors were also excluded. Charlson comorbidity index was used to compare the comorbidities in the groups. The authors also calculated the HAS-BLED score[7] (Uncontrolled Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly>65 years, Drugs/alcohol) to understand the risk of bleeding from anticoagulation in patients with nonvalvular atrial fibrillation. The study was designed as a prospective observational investigation.

Acute upper GIB patients admitted to the hospital with complaints of haematemesis and/or melena underwent laboratory tests for full blood count, creatinine level and international normalised ratio (INR). Following their initial treatment, the patients underwent emergency oesophago-gastroduodenoscopy within the first 24 hours. Peptic ulcers or lesions with blood, clots or flat pigmented hematin were considered signs of acute upper GIB. The endoscopy findings, Charlson comorbidity index scores, number of packed RBCs transfused, number of packed thrombocytes transfused, number of fresh frozen plasma transfused, length of hospital stay, Forrest classification,[2] rate of intensive care unit admission, length of intensive care unit stay, endoscopic treatment, mortality rate, as well as basal haemoglobin, creatinine, haematocrit, platelet, creatinine clearance and INR values at the time of hospital admission were all recorded for the hospitalised patients. The Forrest classification helps assessing the risk of rebleeding. Patients with high-risk ulcers; active spurting (Forrest IA), active oozing (Forrest IB), and nonbleeding visible vessel (Forrest IIA) ulcers should undergo endoscopic therapy. Peptic ulcers with adherent clots (Forrest IIB) should be subjected to endoscopic clot removal. Ulcers with red spots (Forrest IIC) or a clean base (Forrest III) can be observed. The patients were followed up for 30 days or until discharge or death, whichever occurred first. Patients who used warfarin were included in the warfarin group, while patients who used DOACs were included in the DOAC group. The two groups were compared for endoscopy findings, Charlson comorbidity index scores, number of packed RBCs transfused, number of fresh frozen plasma transfused, length of hospital stay, Forrest classification, rate of intensive care unit admission, length of intensive care unit stay, endoscopic treatment, mortality rate, need for nonendoscopic therapy (surgery or interventional radiology), the severity of GIB, and basal haemoglobin, creatinine, haematocrit, platelet, creatinine clearance and INR values at the time of hospital admission. Under the criteria laid down by the International Society on Thrombosis and Hemostasis,[11] major GIB was defined as cases characterised by: 1) The need for the transfusion of two or more units of packed RBCs and 2) a decrease of 2 g/L or greater in the haemoglobin level.

The administration of all drugs promoting NVUGIB was stopped, and all patients received an intravenous proton pump inhibitor as an 80 mg bolus followed by a continuous infusion of 8 mg/h for 48 or 72 hours. Patients with high-risk lesions were treated with clips, thermocoagulation or polidocanol injection. A restrictive RBC transfusion policy was followed according to the clinical guidelines.[1] Patients were transfused when their haemoglobin level fell below 7 g/dl, and a threshold of 8 g/dL was reasonable in patients with preexisting cardiovascular disease and hypotension. Oral anticoagulants were restarted after the bleeding was controlled and oral proton pump inhibitors were added to the treatment.

All statistical analyses were performed by SPSS software (Statistical Package for the Social Sciences, version 20.0, SPSS Inc., Chicago, IL, USA). Descriptive statistics of the study groups were determined as median (min-max) or mean ± standard deviation for continuous variables and counts and percentages for categorical variables. The chi-square test was used to analyse categorical data. The normality of data was checked by the Kolmogorov–Smirnov test. The Mann–Whitney U test was used to compare the differences between groups with non-normal distribution, and the student's t-test was used for continuous variables with normal distribution. The p-values lower than 0.05 were considered statistically significant.

RESULTS

During one year, 346 patients aged 18 years and over were followed up and evaluated for NVUGIB. Table I shows the characteristics of anticoagulant use and indication for anticoagulation in patients with acute nonvariceal upper gastrointestinal bleeding. Of these patients, 52 (15%) were on oral anticoagulant treatment. Out of these 52 patients, 32 (61.5%) were on treatment with nonvitamin K antagonists, named as DOACs (DOAC group), and 20 (38.5%) were on treatment with a vitamin K antagonist, named as warfarin (warfarin group). The demographics, baseline laboratory values, endoscopic findings, and hospital outcomes of the patients were presented in Table II. Timing from starting oral anticoagulants to bleeding was 30 (3-3350) days in warfarin group and 11 (2-2135) days in DOAC group (p=0590). Two patients in DOAC group and 1 patient in warfarin group had severe or moderate renal impairment (creatinine clearance <50 mL/min).

Table I: Characteristics of anticoagulant use and indication for anticoagulation in patients with acute nonvariceal upper gastrointestinal bleeding.

Anticoagulant	Warfarin (n=20)	DOAC (n=32)
		Rivaroxaban (n=16, 50.000%) (n=14,20 mg/gun) (n=2,15mg/gun) Edoxaban (n=11, 34.375 %) (60mg/gun) Apixaban (n=4, 12.500%) (10 mg/gun) Dabigatran (n=1, 3.125%) (300 mg/gün)
Indication		
CAD	1(5%)	7(21.875%)
CVA	2(10%)	1(3.125%)
AF	3(15%)	22(68.750%)
	HAS-BLED score:1.66±0.57	HAS-BLED score:1.64±0.58
Knee replacement	0	1(3.125%)
VHD	14(70%)	1(3.125%)

CAD: Coronary artery disease, CVA: Cerebrovascular accident, AF: Nonvalvular atrial fibrillation, VHD: Valvular heart disease.

Table II: Demographics, baseline laboratory values, endoscopic findings, and hospital outcomes of patients with acute nonvariceal upper gastrointestinal bleeding.

	Warfarin (n=20)	DOAC (n=32)	p-value
Age, years***	70.65±12.56	72.69±11.48	0.560
Male**	13 (65%)	20 (62.5%)	>0.5
Female**	7 (35%)	12 (37.5%)	>0.5
INR* (0.8-1.3)	6.08 (0-13.7)	1.4 (1-2.81)	**<0.001**
Haemoglobin (g/dL) ***(13.5-18)	7.17±1.64	7.05±1.81	0.804
Haematocrit (%)*** (42-52)	22.41±5.02	21.91±4.89	0.722
Platelet count,10^3/µL*** (150-450)	225.80±73.66	288.66±142.79	0.042
Creatinine,mg/dL* (0.7-1.2)	1.20 (0.6-1.9)	1.25 (0.71-3.7)	0.211
Creatinine clearance,ml/min*** (90-150)	60.10±26.87	49.94±23.40	0.172
OGD findings			
Duodenal ulcer	10, 50%	8, 25%	
Gastric ulcer	4, 20%	10, 31.25%	
Gastroduodenal erosions	5, 25%	10, 31.25%	
Erosion+oesophagitis	1, 5%	3, 9.375%	
Mallory-weiss tears	0	1, 3.125%	
Forrest classification			
2a	2	1	
2c	3	0	
3	8	18	
Endoscopic therapy			
Injection+heater probe	1	0	
Injection+clips	0	2	
Injection	1	0	
Number of pRBC transfused, units *	3 (0-6)	3 (0-10)	0.229
FFP transfusion,units*	3 (0-8)	0 (0-3)	**<0.001**
LOS,days *	5 (3-10)	4.5 (2-20)	0.739
ICU admission**	9 (45)	10 (31)	0.321
ICU LOS,days*	2 (1-6)	4 (1-11)	0.083
CCI, points *	5.5 (1-11)	6 (1-9)	0.592
Major bleeding**	14/20 (70%)	25/32 (78%)	0.529
Mortality**	1/20 (5 %)	1/32 (3%)	0.579
Timing for anticoagulants initiation, days*	30 (3-3350)	11 (2-2135)	0.590

DOAC: Direct oral anticoagulant, OGD: Oesophago-gastroduodenoscopy FFP: Fresh frozen plasma, LOS: Length of hospital stay, ICU: Intensive care unit, CCI: Charlson comorbidity. Index, pRBC: Packed red blood cell, NVUGIB: Non-variceal upper gastrointestinal bleeding INR: International normalised ratio. Applied tests:: Mann whitney U-test, median (min-max); **:Chi-square test, number (percentage); *** student t test, mean ± standard deviation.*

In DOAC group, dose adjustments were done for patients with severe or moderate renal impairment. Oesophago-gastroduodenoscopy showed that the most common lesions observed were duodenal ulcers in warfarin group and gastric ulcers and gastroduodenal erosion in DOAC group. Patients in the two groups were similar in age and gender. Warfarin group and DOAC group comprised senile patients (70.65±12.56; 72.69±11.48, p=0.560, respectively), and male patients presented with a higher rate of NVUGIB (13 males and 7 females, 65% and 35%; 20 males and 12 females, 62.5% and 37.5%, respectively). The number of packed RBCs transfused, length of hospital stay, initial numbers of patients admitted to the intensive care unit, major bleeding and Charlson comorbidity index scores were

similar in the DOAC and warfarin groups. As expected, the need for the transfusion of fresh frozen plasma was greater in group warfarin [median 3 units (0-8) and 0 units (0-3), respectively; p<0.001]. Although the intensive care unit length of stay was longer in the DOAC group than in the warfarin group, the difference between the groups was statistically insignificant, and the p-value was close to 0.05 [median 4 days (1-11), median 2 days (1-6); p=0.083]. Neither mortality nor a need for nonendoscopic therapy (surgery or interventional radiology) was observed in the two groups. No statistically significant difference was observed between group warfarin and group DOAC for haemoglobin, platelet, haematocrit, creatinine and creatinine clearance values.

DISCUSSION

Warfarin's unpredictable anticoagulant effects, which require continuous laboratory monitoring, have brought about the development of novel oral anticoagulants as an alternative. Since 2010, several DOACs have been approved for use in the prevention of venous thromboembolism- and nonvalvular atrial fibrillation-related stroke.[12-14] These DOACs, which include direct thrombin inhibitors (dabigatran) and factor Xa inhibitors (rivaroxaban, apixaban, and edoxaban), offer a better safety and efficacy profile than vitamin K antagonists such as warfarin.[14] Unfortunately, similar to warfarin, the most significant side effect of DOACs is GIB, which may be of mild, moderate or life-threatening severity.[15,16] A meta--analysis showed that in comparison to standard treatment, DOACs increased the risk of GIB[17] and the other prospective cohort study revealed that 20% of all oral anticoagulants-related bleeding events were determined to be upper GIB.[18] In another study carried out in Japan, in which 3237 patients who were treated with either warfarin or DOACs were monitored for a median period of 39.3 months, GIB was determined to have occurred in 68 patients (2.1%).[19] Based on the evaluation of real-life data, Albrecht *et al*. [20] reported that the most common type of DOAC-related GIB was upper GIB. Consistent with the literature,[20,21] The present study demonstrated that patients using oral anticoagulants (DOAC or warfarin) accounted for 15% of all acute NVUGIB cases.

Literature reports providing data on the risk of GIB associated with DOACs, compared to warfarin, are controversial. An early report by Holster *et al*. on DOACs suggested that these new generation anticoagulants increased GIB.[17] Recent studies have reported that the risk of GIB associated with the use of DOACs does not exceed the risk associated with the use of warfarin.[19-20] A study has shown that in the past 23 years, the features and aetiology of upper GIB have changed. The increased use of DOACs as of 2010 is considered to be associated with a progressively increasing occurrence of upper GIB.[5] In the present study, 15% of all patients diagnosed with NVUGIB were determined to use anticoagulants, supporting this opinion. In their research on patients diagnosed with atrial fibrillation, Murata *et al*. determined that 51.2% of the patients (n=1676) used DOACs and 48.8% (n=1561) used warfarin.[19] Among these patients, 68 (2.1%) (n=36 of warfarin users and n=32 of DOAC users) developed GIB. Out of the 68 patients with GIB, 32 (n=17, 53.1% of warfarin users; n=15, 46.9% of DOAC users) presented with upper GIB. Similarly, Albrecht *et al*. reported that GIB was less common in DOAC users than in vitamin K antagonist users.[20] In contrast, in the present study, majority of patients diagnosed with anticoagulant-related upper GIB were DOAC users (n=32/52; 61.5%).

The above-mentioned studies have been evaluated the data 5 and 8 years ago, and the present study reflects the present day trends. The use of DOAC has increased more than warfarin in the last 10 years, and therefore, GIB may have been detected relatively more frequently in patients using DOAC. Lee *et al*. reported that DOACs were less associated with upper GIB than warfarin in patient groups similar for age, gender and comorbidities.[22] However, the most important difference that distinguished the older study from the present study was that they included patients using oral anticoagulants in combination with proton pump inhibitors.

In a retrospective study by Brodie *et al*.,[23] which investigated patients with GIB known to use DOACs and warfarin, no significant difference was determined for age, gender or comorbidity. The most common localisation of GIB was the upper region of the gastrointestinal tract, and when compared to warfarin users, DOACs users were hospitalised for a shorter period, showed less need for blood transfusion, and presented with a lower rate of severe bleeding. This study's design was different from the present study. The authors evaluated only upper GIB but Brodie *et al*. investigated patients with all kinds of GIB (upper, lower, anorectal, small bowel, and indeterminate).[23] In another recent retrospective study, like the present study, no statistically significant increase was observed in the need for RBC transfusion, hospitalisation duration or mortality of oral anticoagulant users compared to patients not treated with oral anticoagulants.[24] Moreover, the subgroup analysis of this study demonstrated that warfarin and DOAC users showed no significant difference in mortality and RBC transfusion, and although the hospitalisation duration of DOAC users was longer, this difference was statistically insignificant.

There are only very few available studies on the effects of DOACs on the hospitalisation duration and need for RBC transfusion of patients with upper GIB. The present study, which aimed to provide data on this particular subject, demonstrated that warfarin and DOAC users, who were similar in age, gender, and comorbidity, also displayed similarities in hospitalisation duration, intensive care admission, mortality, and the need for RBC transfusion. While intensive care unit duration was longer in DOAC users with a p-value very close to 0.05, the difference among warfarin users was

statistically insignificant. If the number of patients included in the study was higher, the difference could have been statistically significant. Use of fresh frozen plasma as an antidote to warfarin might have been effective in this result.

In a previous study, investigating intensive care unit duration in warfarin users, compared to rivaroxaban and dabigatran users. Similar to the present study, it was ascertained that there was no statistically significant difference between the groups for the number of patients admitted to the intensive care unit.[25] Unlike the present study, this study included patients with atrial fibrillation who were hospitalised for bleeding after starting warfarin, dabigatran, or rivaroxaban. In agreement with available literature data,[12] it was observed that the majority of NVUGIB cases involved major bleeding. Although recent reports have suggested that GIB in DOAC users may be less severe than that observed in warfarin users.[23] They included all GIB but the present study included only patients with upper GIB. However, in the present study, no statistically significant difference was found between patients using DOACs and warfarin users for major NVUGIB. The present study had some limitations arising from the relatively small sample size and the short duration of follow-up.

CONCLUSION

Evaluation of NVUGIB in warfarin and DOACs users, who were similar in comorbidity, age, and gender, demonstrated no statistically significant difference in major bleeding, length of hospital stay, intensive care unit admission, and need for RBC transfusion.

ETHICAL APPROVAL:
The study protocol (2020.241.11.01) was approved by the Ethics Committee at Tekirdag Namik Kemal University.

PATIENTS' CONSENT:
Informed consent were obtained from all individual participants included in the study.

COMPETING INTEREST:
The authors declared no competing interest.

AUTHORS' CONTRIBUTION:
TS, HK: Conceived and designed the study and wrote the manuscript.
NTK, HK: Contributed to the analysis and interpretation of data.
MA, RM: Revised the manuscript.
All the authors have approved the final version of the manuscript to be published.

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