Original Article

Bleeding Events in the Emergency Department with Warfarin versus Novel Oral Anticoagulants: A Five-year Analysis

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Abstract

Background: Although warfarin is the most effective treatment approved to prevent atrial fibrillation-associated stroke, it remains underused in clinical practice due to patient noncompliance. Therefore, novel oral anticoagulants (NOACs) have been developed. **Aims:** This study aimed to identify bleeding complications in patients who were taking oral anticoagulants and compare the rates of major and minor bleeding events between NOACs and warfarin groups. **Patients and Methods:** We conducted a retrospective, observational study of warfarin- and NOAC-treated patients who presented to an emergency department between January 2015 and December 2019 with bleeding events. We compared patients with major and minor bleeding in terms of age, gender, comorbid diseases, type of anticoagulant, and site of bleeding. **Results:** An electronic search yielded 95 (21.9%) cases of patients taking a NOAC (i.e., dabigatran [19], rivaroxaban [45], apixaban [29], or edoxaban [6]) and 354 taking warfarin. There were no significant differences between the warfarin and NOACs groups in the frequency of minor bleeding complications. Similarly, there were no significant differences between the groups in the frequency of major bleeding complications. No significant difference in intracranial bleeding was seen between the NOACs- and warfarin-treated patients, although the incidence of gastrointestinal bleeding was significantly higher in the NOACs ($P = 0.102$ and $P = 0.021$, respectively). **Conclusion:** Our findings indicate that rates of major and minor bleeding complications in patients taking NOACs are similar to those in patients taking warfarin. While warfarin was associated with fewer complications than NOACs in terms of gastrointestinal bleeding, the risk of intracranial bleeding, was similar between the groups.

Keywords: *Anticoagulants, bleeding events, NOACs, warfarin*

Received: 15-Feb-2022;
Revision: 18-May-2022;
Accepted: 25-May-2022;
Published: 16-Aug-2022

Introduction

Warfarin is a vitamin K antagonist (VKA) that has been used for over 50 years to prevent atrial fibrillation (AF)-associated stroke.[1] Although warfarin is the most effective treatment approved to prevent ischemic stroke in patients with AF, it remains underused in clinical practice due to patient noncompliance. Therefore, novel oral anticoagulants (NOACs), also known as non-vitamin K or direct oral anticoagulants, have been developed.[2] Among these, dabigatran binds reversibly to the thrombin molecule, whereas rivaroxaban, apixaban, and edoxaban directly inhibit factor Xa.[3] Following the results of several randomized trials, including the "Randomized Evaluation of Long-Term Anticoagulation Therapy" (RE-LY) trial (dabigatran), "Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation" (ROCKET AF; rivaroxaban), "Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation" (ARISTOTLE)

Access this article online

Quick Response Code:

Website: www.njcponline.com

DOI: 10.4103/njcp.njcp_125_22

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How to cite this article: Dogan Y, Az A, Sogut O, Akdemir T, Kaplan O. Bleeding events in the emergency department with warfarin versus novel oral anticoagulants: A five-year analysis. Niger J Clin Pract 2022;25:1308-17.

trial (Apixaban), and "Edoxaban once daily to prevent stroke or systemic embolism in patients with atrial fibrillation (ENGAGE AF-TIMI 48) trial (edoxaban), NOACs were approved by the United States Food and Drug Administration (FDA).[4–7]

Important advantages of NOAC agents compared to VKAs include higher patient compliance, no requirement for dose adjustment or routine testing of the prothrombin time/international normalized ratio (PT/INR), reduced risk of intracranial bleeding, lack of dietary interactions, and markedly reduced susceptibility to drug interactions.[8–10] When NOACs were first introduced, their efficacy for treating hemorrhage was unknown. The first NOACs released to the market were developed based on data on complications.[8] In 2010, the FDA approved the first direct oral anticoagulant (dabigatran) for prophylaxis of stroke in patients with non-valvular AF; this agent was considered revolutionary, whereas VKA (warfarin) had been the only oral anticoagulant available for several decades. Thereafter, the FDA approved the factor Xa inhibitors rivaroxaban, apixaban, and edoxaban.[11,12] The use of NOACs is increasing in daily practice. Although NOACs are associated with a higher risk of gastrointestinal bleeding, they carry a lower risk of major bleeding and fatal bleeding compared to VKAs.[3]

This study compared the rates of major and minor bleeding events between patients taking NOACs and VKAs (including warfarin) who were admitted to the emergency department (ED).

Patients And Methods

We conducted a retrospective observational study of VKA (warfarin)- and NOACs-treated (e.g., (rivaroxaban, apixaban, edoxaban, or dabigatran) Turkish patients presenting to a large academic ED between January 2015 and December 2019 with bleeding events.

Study groups

All cases meeting the eligibility criteria during the study period were included to reduce selection bias. We identified 24,774 adult patients (>18 years old) diagnosed with non-traumatic bleeding (major or minor bleeding) through the hospital's automated systems and archives between January 2015 and December 2019. Of these patients, 495 were also taking warfarin or a NOAC. Twenty-five patients who were using warfarin were excluded from the study because their PT/INR was <1.5. Fourteen patients with AF and coronary artery disease (CAD), who were receiving concurrent oral anticoagulants-antiplatelet therapy that may increase bleeding risk were excluded from the study. Three other patients were excluded because they had a history of hemorrhage due to accidental consumption of high doses of someone else's prescription medication. Finally, 453 patients who presented with any bleeding event due to warfarin or NOACs were included in the study. We determined that 204 patients had major, and 150 minor, bleeding associated with warfarin use, while 63 patients had major, and 39 patients minor, bleeding associated with NOACs use. The flow chart shows the patient-selection process [Figure 1].

Ethical considerations

This retrospective, single-center clinical study was conducted in accordance with the 1989 Declaration of Helsinki and was approved by the Institutional Review Board of Haseki Research and Training Hospital in Istanbul, Turkey (no. 2020-145).

Data collection

We assessed patients' demographic information (age and sex), vital signs on admission (systolic blood pressure [SBP], SpO_2, heart rate [HR], and body temperature), physical examination findings, comorbidities (hypertension [HT], diabetes mellitus [DM], chronic renal failure [CRF], and **CAD**), medications used, indications for anticoagulant therapy (AF, pulmonary thromboembolism [PTE], deep vein thrombosis [DVT], mechanical valve replacement [MVR], ischemic stroke), laboratory parameters (including hematological findings; hemoglobin and platelet counts), and biochemical and coagulation findings (creatinine, PT/INR, and activated partial thromboplastin time [aPTT]).

Gastrointestinal, retroperitoneal, cranial, and intraabdominal bleeding, as well as bleeding causing a 2-unit decrease in hemoglobin levels and bleeding requiring transfusion of >3 units of packed red blood cells (PRBCs), were defined as major bleeding events. Skin ecchymosis, skin hematomas >25 cm^2, spontaneous epistaxis for >5 minutes, and gingival bleeding for >5 minutes were defined as clinically significant minor bleeding. We compared the major and minor bleeding complications between patients using warfarin and those using NOACs. Additionally, we evaluated 30-day mortality rates associated with life-threatening major bleeding in patients using NOACs and warfarin.

Data analysis

All data analyses were conducted using SPSS statistical software (version 15.0 for Windows; SPSS Inc., Chicago, IL, USA). Numerical data are expressed as means ± standard deviations or medians with minimum and maximum values. Categorical variables (sex and age) are expressed as numbers (n) and percentages (%). Group data were analyzed using the Chi-squared test for normally distributed data and the Mann–Whitney U test

with Bonferroni correction for non-normally distributed data. Independent variables were analyzed using multivariate logistic regression analysis. The threshold for statistical significance was defined as $P < 0.05$.

Results

We identified 453 patients who presented to our ED with any bleeding event and were taking warfarin (n = 354) or a NOAC (dabigatran [19], rivaroxaban [45], apixaban [29], edoxaban [6]). Table 1 shows the distribution of bleeding events according to oral anticoagulant type.

Table 1: Bleeding events according to anticoagulant type

	n	%
Warfarin	354/453	78.10
NOACs	99/453	21.90
Dabigatran	19	4.19
Rivaroxaban	45	9.96
Apixaban	29	6.42
Edoxaban	6	1.33

Data are expressed as number (*n*) and percentage (%). NOACs, novel oral anticoagulants

Bleeding events associated with warfarin use were observed in 69 (15.23%) patients in 2015, 93 (20.53%) in 2016, 75 (15.55%) in 2017, 72 (15.89%) in 2018, and 45 (9.93%) in 2019. Bleeding events associated with NOACs use were seen in 8 (1.76%) patients in 2015, 12 (2.64%) in 2016, 15 (3.31%) in 2017, 24 (5.29%) in 2018, and 40 (8.83%) in 2019. Figure 2 shows the rates of bleeding events according to oral anticoagulant type by year.

No significant differences were observed between the warfarin and NOAC groups in the frequency of minor

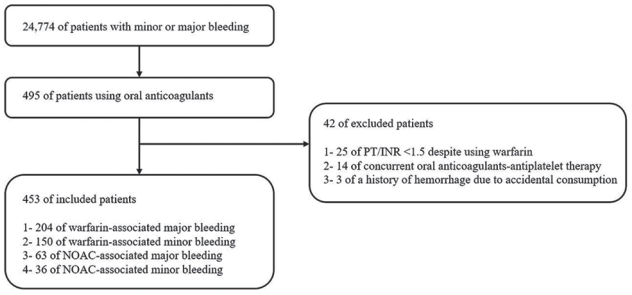

Figure 1: Flowchart

Table 2: Demographic characteristics, indications, comorbidities, and laboratory findings by type of anticoagulant in patients with minor bleeding

Characteristic	Warfarin *n* (%)	NOACs *n* (%)	*P**
Patients with minor bleeding/all patients	150/354 (42.4)	36/99 (36.4)	0.283
Age, years (mean±SD)	70±12.78	79±8.47	<0.001
Male/female ratio	78/72	17/19	0.890
Indications for anticoagulant therapy			
AF	77 (51.3)	34 (94.4)	<0.001
PTE	12 (8.0)	1 (2.8)	0.468
DVT	7 (4.7)	1 (2.8)	1.000
MVR	50 (33.3)	0 (0.0)	-
Stroke	4 (2.7)	0 (0.0)	1.000
Comorbidities	70 (46.7)	24 (66.7)	0.031
Laboratory findings	Mean±SD	Mean±SD	*P**
Hemoglobin (g/dL)	11.78±2.81	11.16±2.70	0.137
Platelet (10≥/µL)	251.62±85.38	242.88±156.57	0.086
e-GFR (ml/min/1.73 m²)	70.22±28.69	61.02±22.33	0.053
Creatinine (mg/dL)	1.15±0.62	1.15±0.56	0.501
PT/INR (seconds)	4.11±1.65	1.31±0.50	<0.001
aPTT (seconds)	57.42±25.59	31.98±9.50	<0.001
Minor bleeding types	*n* (%)	*n* (%)	*P**
Ecchymosis	15 (10.0)	1 (2.8)	0.317
Epistaxis	39 (26.0)	12 (33.3)	0.376
Hematuria	70 (46.7)	22 (61.1)	0.120
Hematoma	10 (6.7)	0 (0.0)	0.213
Gingival bleeding	13 (8.7)	0 (0.0)	0.076
Genital bleeding	3 (2.0)	1 (2.8)	0.580

Data are expressed as number (*n*) and percentage (%) or mean±standard deviation (SD). *Subgroup analyses (warfarin vs. NOACs) were conducted using Chi-squared and Mann–Whitney U tests, as appropriate. NOACs, novel oral anticoagulants; Comorbidities include hypertension, diabetes mellitus, chronic renal failure, and coronary artery disease; AF, atrial fibrillation; PTE, pulmonary thromboembolism; DVT, deep vein thrombosis; MVR, mechanical valve replacement; e-GFR estimated glomerular filtration rate; PT/INR, prothrombin time/international normalized ratio; aPTT, activated partial thromboplastin time

Table 3: Demographic characteristics, indications, comorbidities, and laboratory findings by type of anticoagulant in patients with major bleeding

Characteristic	Warfarin *n* (%)	NOACs *n* (%)	*P**
Patients with major bleeding/all patients	204/354 (57.6)	63/99 (63.6)	0.283
Age, years (mean±SD)	71±12.45	80±8.62	<0.001
Male/female ratio	98/106	33/30	0.547
Indications for anticoagulant therapy			
AF	84 (41.2)	58 (92.0)	<0.001
PTE	3 (1.5)	0 (0)	1.000
DVT	6 (2.9)	0 (0)	0.341
MVR	108 (52.9)	0 (0.0)	-
Stroke	3 (1.5)	5 (8.0)	0.020
Comorbidities	131 (64.2)	49 (77.8)	0.045
Laboratory findings	Mean±SD	Mean±SD	*P**
Hemoglobin (g/dL)	9.09±3.10	8.40±2.53	0.194
Platelet (10≥/µL)	266.85±81.51	263.36±115.62	0.249
e-GFR (ml/min/1.73 m²)	61.74±29.62	52.34±20.94	0.024
Creatinine (mg/dL)	1.37±1.01	1.29±0.42	0.125
PT/INR (seconds)	3.98±1.75	1.38±0.61	<0.001
aPTT (seconds)	53.58±25.39	32.63±14.52	<0.001
Major bleeding types	*n* (%)	*n* (%)	*P**
Gastrointestinal bleeding	162 (79.4)	58 (92.1)	0.021
Intracranial bleeding	33 (16.2)	5 (7.9)	0.102
Rectus sheath hematoma	9 (4.4)	0 (0.0)	0.121

Data are expressed as number (*n*) and percentage (%) or mean±standard deviation (SD). *Subgroup analyses (warfarin vs. NOAC) were conducted using Chi-squared and Mann–Whitney U tests, as appropriate. NOACs, novel oral anticoagulants; Comorbidities include hypertension, diabetes mellitus, chronic renal failure, and coronary artery disease; AF, atrial fibrillation; PTE, pulmonary thromboembolism; DVT, deep vein thrombosis; MVR, mechanical valve replacement; e-GFR estimated glomerular filtration rate; PT/INR, prothrombin time/international normalized ratio; aPTT, activated partial thromboplastin time

Table 4: Major and minor bleeding events by type of anticoagulant in patients with atrial fibrillation

Characteristic	Warfarin *n* (%)	NOACs *n* (%)	*P**
Major bleeding in anticoagulated patients with AF/anticoagulated patients	84/161 (52.2)	58/92 (63.0)	0.008
Minor bleeding in anticoagulated patients with AF/anticoagulated patients	77/161 (47.8)	34/92 (36.7)	0.153
Major bleeding types	*n* (%)	*n* (%)	
Gastrointestinal bleeding	59 (70.2)	53 (91.4)	
Intracranial bleeding	21 (25.0)	5 (8.6)	
Rectus sheath hematoma	4 (4.8)	0 (0)	
Minor bleeding types	n (%)	n (%)	
Ecchymosis	7 (9.1)	1 (2.9)	
Epistaxis	22 (28.5)	12 (35.3)	
Hematuria	38 (49.3)	21 (61.8)	
Hematoma	4 (5.2)	0 (0.0)	
Gingival bleeding	6 (7.9)	0 (0.0)	

Data are expressed as number (*n*) and percentage (%). *Subgroup analyses (warfarin vs. NOACs) were conducted using Chi-squared test. NOACs, novel oral anticoagulants; AF, atrial fibrillation

bleeding or gender (42.4% vs. 36.4%, $P = 0.283$ and $P = 0.890$, respectively) [Table 2]. Similarly, there were no significant differences between the groups in

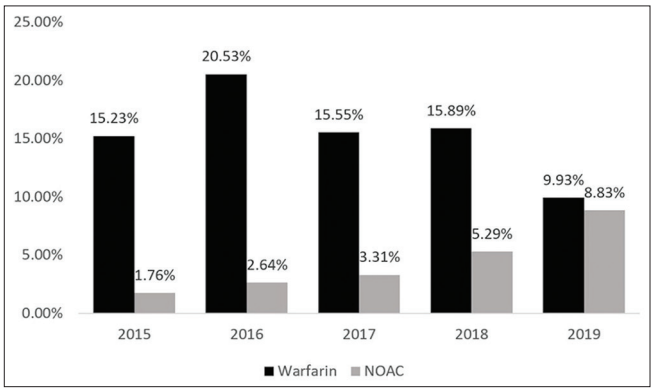

Figure 2: Rate of bleeding events by year according to oral anticoagulant

the frequency of major bleeding or gender (57.6% vs. 63.6%, $P = 0.283$ and $P = 0.547$, respectively) [Table 3]. Additionally, patients with minor or major bleeding who were taking NOACs were significantly older than those taking warfarin (both $P < 0.001$) [Tables 2 and 3].

When the patients with minor bleeding were evaluated in terms of indications for anticoagulation, no significant differences were observed between the warfarin and NOAC groups in their use of anticoagulants for PTE, DVT, and ischemic stroke ($P = 0.468$, $P = 1.000$ and $P = 1.000$, respectively) [Table 2]. However, significantly

Table 5: Comparison of age, sex, comorbidities, laboratory findings and types of anticoagulant between survivors and non-Survivors

Characteristic	Survivors *n* (%)	Non-survivors *n* (%)	*P**
Number of patients/all patients	428/453 (94.5)	25/453 (5.5)	
Age, years (mean±SD)	72±12.33	79±11.26	0.004
Male/female ratio	210/218	16/9	0.147
Comorbidities			
CAD	102 (23.8)	6 (24.0)	0.985
HT	189 (44.2)	15 (60.0)	0.122
DM	100 (23.4)	6 (24.0)	0.942
CRF	78 (18.2)	6 (24.0)	0.435
Laboratory findings	Mean±SD	Mean±SD	*P**
Hemoglobin (g/dL)	10.03±3.17	10.30±3.67	0.721
Platelet (10≥/µL)	258.80±95.39	270.00±105.49	0.566
e-GFR (ml/min/1.73 m²)	63.83±28.20	52.00±28.83	0.044
Creatinine (mg/dL)	1.25±0.80	1.57±0.88	0.032
PT/INR (seconds)	3.40±1.90	3.46±1.82	0.299
aPTT (seconds)	49.46±24.22	61.83±36.49	0.154
Oral anticoagulant types	Mean±SD	Mean±SD	*P**
Warfarin	335 (78.3)	19 (76.0)	0.789
NOACs	93 (21.7)	6 (24.0)	
Dabigatran	16 (3.7)	3 (12.0)	0.080
Rivaroxaban	43 (10.0)	2 (8.0)	1.000
Apixaban	28 (6.5)	1 (4.0)	1.000
Edoxaban	6 (1.4)	0 (0.0)	1.000

Data are expressed as number (n) and percentage (%) or mean±standard deviation (SD). *Subgroup analyses (survivors vs. non-survivors) were conducted using Chi-squared and Mann–Whitney U tests, as appropriate. CAD, coronary artery disease; HT, hypertension; DM diabetes mellitus; CRF chronic renal failure; e-GFR estimated glomerular filtration rate; PT/INR prothrombin time/international normalized ratio; aPTT, activated partial thromboplastin time; NOACs novel oral anticoagulants

Table 6: Independent predictors of mortality identified in multivariate logistic regression analysis using the enter backward methods

Enter method	*P*	OR	95% CI
Age (years)	0.024	1.060	1.008-1.115
Gender (male)	0.096	2.236	0.866-5.772
CAD	0.617	0.761	0.260-2.223
HT	0.160	1.968	0.766-5.056
DM	0.945	1.039	0.351-3.073
CRF	0.731	1.249	0.351-4.442
Hemoglobin	0.154	1.115	0.960-1.295
Platelet	0.357	1.002	0.998-1.007
e-GFR	0.933	0.999	0.970-1.029
Creatinine	0.588	1.212	0.606-2.424
PT/INR	0.933	1.015	0.725-1.419
aPTT	0.446	1.009	0.986-1.033
Apixaban	0.232	0.220	0.018-2.631
Rivaroxaban	0.226	0.278	0.035-2.215
Edoxaban	0.999	0	0
Dabigatran	0.234	2.933	0.499-17.231
Warfarin	0.234	0.341	0.058-2.003
Backward method			
Age (years)	0.005	1.061	1.019-1.106
Gender (male)	0.042	2.485	1.032-5.983
aPTT	0.050	1.011	1.000-1.023

OR, odds ratio; CI confidence interval. CAD coronary artery disease; HT hypertension; DM diabetes mellitus; CRF, chronic renal failure; e-GFR estimated glomerular filtration rate; PT/INR prothrombin time/international normalized ratio; aPTT activated partial thromboplastin time

more patients with minor bleeding were taking NOACs than warfarin due to AF ($P < 0.001$) [Table 2].

Comorbid diseases were significantly more prevalent among the NOACs than warfarin patients with minor bleeding ($P = 0.031$) [Table 2]. No significant differences were observed between groups in mean hemoglobin, platelet, e-GFR, or creatinine values ($P = 0.137$, $P = 0.086$, $P = 0.053$, and $P = 0.501$, respectively) [Table 2]. However, the mean serum PT/INR and aPTT values were significantly higher in patients with minor bleeding associated with warfarin compared to those with minor bleeding associated with NOACs (both $P < 0.01$) [Table 2]. There were no significant differences between the warfarin and NOAC groups in the rates of minor bleeding complications such as ecchymosis, epistaxis, hematuria, hematoma, gingival bleeding, and genital bleeding ($P = 0.317$, $P = 0.376$, $P = 0.120$, $P = 0.213$, $P = 0.076$, and $P = 0.580$, respectively) [Table 2].

When patients who had major bleeding while taking warfarin or NOACs were evaluated according to the indications for anticoagulation, no significant differences were found in the rate of use of anticoagulants for PTE and DVT ($P = 1.000$ and $P = 0.341$, respectively) [Table 3]. Moreover, significantly more patients with major bleeding were taking NOACs compared to warfarin due to AF and ischemic stroke ($P < 0.001$ and $P = 0.020$, respectively) [Table 3].

Comorbid diseases among patients with major bleeding were significantly more common in the NOACs than the warfarin group ($P = 0.045$) [Table 3]. There were no significant differences between the groups in mean hemoglobin, platelet, e-GFR, or creatinine values ($P = 0.194$, $P = 0.249$, and $P = 0.125$, respectively) [Table 3]. However, the mean serum e-GFR, PT/INR, and aPTT values were significantly higher among patients with major bleeding associated with warfarin compared to those with major bleeding associated with NOACs ($P = 0.024$, $P < 0.01$, and $P < 0.01$, respectively) [Table 3].

There was no significant difference between the warfarin and NOAC groups in the rates of major bleeding complications, such as intracranial bleeding and rectus sheath hematoma (P = 0.102 and P = 0.121, respectively) [Table 3]. However, the rate of gastrointestinal bleeding was significantly higher in the NOACs compared to the warfarin group (P = 0.021) [Table 3].

Subgroup analysis revealed that there was no significant difference between warfarin-treated patients and NOACs-treated patients due to AF in the rates of minor bleeding complications (47.8% vs. 36.7%, P = 0.153) [Table 4]. However, the rates of major bleeding complications were significantly higher among AF patients treated with NOACs compared to those treated with warfarin (63.0% vs. 52.2%, P = 0.008) [Table 4].

In total, 25 patients, including 16 men (64.0%) and 9 women (36.0%), died within 30 days. The mean age of non-surviving patients was significantly higher than that of surviving patients (79 ± 11.26 vs. 72 ± 12.33 years, P = 0.004) [Table 5]. There was no significant difference in gender between the surviving and non-surviving groups (P = 0.147) [Table 5].

No significant differences were found between the surviving and non-surviving groups in mean hemoglobin, platelet, PT/INR, or aPTT values (P = 0.721, P = 0.566, P = 0.299, and P = 0.154, respectively) [Table 5]. However, the mean e-GFR value was significantly lower among non-surviving than surviving patients (52.00 ± 28.83 vs. 63.83 ± 28.20, P = 0.044) [Table 5]. In addition, the mean creatinine value was significantly higher among non-surviving than surviving patients (1.57 ± 0.88 vs. 1.25 ± 0.80, P = 0.032) [Table 5]. The rates of comorbidities including CAD, HT, DM, and CRF did not differ significantly between surviving and non-surviving patients (P = 0.985, P = 0.122, P = 0.942, and P = 0.435, respectively) [Table 5]. When surviving and non-surviving patient groups were evaluated according to the type of oral anticoagulant used, there was no significant difference between survivors and non-survivors in rates of warfarin and NOACs use (P = 0.789) [Table 5]. Similarly, there were no significant differences between the groups in their use of individual NOACs, i.e., dabigatran, rivaroxaban, apixaban, and edoxaban (P = 0.080, P = 1.000, P = 1.000, and P = 1.000, respectively) [Table 5].

In the multivariate logistic regression analysis, the enter method demonstrated that older age (odds ratio [OR], 1.060, confidence interval [CI]: 1.008–1.115, P = 0.024) remained an independent predictor of mortality in patients who had bleeding complications associated with oral anticoagulants [Table 6]. In addition, the backward method demonstrated that older age (OR, 1.061, CI: 1.019–1.106, P = 0.005), male gender (OR, 2.485, 95% CI: 1.032–5.983, P = 0.042), and aPTT values (OR, 1.011, 95% CI: 1.000–1.023, P = 0.050) remained independent predictors of mortality in patients who had bleeding complications associated with oral anticoagulants [Table 6].

Discussion

The key findings of this study were as follows. First, among the 453 patients with major or minor bleeding complications associated with oral anticoagulant use, the most commonly used drug was warfarin (n = 354; 78.10%). Second, although the mean age of patients who exhibited minor bleeding was significantly higher among those using NOACs than among those using warfarin, the overall rate of minor bleeding complications was similar in both groups. Third, the rates of minor bleeding (ecchymosis, epistaxis, hematuria, hematoma, gingival bleeding, and genital bleeding) did not differ significantly between the warfarin and NOACs groups. Fourth, among patients who exhibited major bleeding, the mean age of those using NOACs was significantly higher than that of those using warfarin. Fifth, we found no statistically significant difference between the warfarin and NOACs groups in the rates of major bleeding events, including intracranial bleeding and rectus sheath hematoma. However, the rate of gastrointestinal bleeding was significantly increased in patients using NOACs compared to those using warfarin. Sixth, no significant difference was observed between warfarin-treated patients and NOACs -treated patients due to AF in the rates of minor bleeding complications. However, there was a significant difference between warfarin-treated patients and NOACs-treated patients due to AF in the rates of major bleeding complications. Seventh, the mean e-GFR value was significantly lower among non-surviving patients (30-day mortality) using an oral anticoagulant than among surviving patients (30-day survival). In addition, the mean creatinine value and age were significantly higher for non-surviving compared to surviving patients. Eighth, in multivariate logistic regression analysis, older age and male gender remained independent predictors of mortality in patients who had minor or major bleeding events associated with oral anticoagulants.

Dabigatran was the first NOAC approved by the FDA (in 2010) to prevent thromboembolic events in patients with non-valvular AF. This was followed by rivaroxaban (2011), apixaban (2012), and

edoxaban (2015).[13–16] Important advantages of NOACs compared to VKAs include no requirement for dose adjustment or routine PT/INR testing and markedly reduced susceptibility to drug interactions.[17] In our study, warfarin-related bleeding was observed in 69 patients in 2015, 93 in 2016, 75 in 2017, 72 in 2018, and 45 in 2019 (15.23%, 20.53%, 15.55%, 15.89%, and 9.93%, respectively). In addition, 8 patients had NOACs-related bleeding complications in 2015, 12 in 2016, 15 in 2017, 24 in 2018, and 40 in 2019 (1.76%, 2.64%, 5.29%, and 8.83%, respectively). The increase in NOACs-related bleeding rates over the years may be associated with increased use of NOACs. Also, in our study, the mean PT/INR value of patients using NOACs was significantly lower than that of patients using warfarin, and was close to the normal reference range (1.38 ± 0.61 vs. 3.98 ± 1.75; $P < 0.001$). This outcome, similar to previous research,[17] supports the conclusion that PT/INR follow-up is not required in patients using NOACs.

The literature includes several double-blind, randomized multicenter studies comparing NOACs with warfarin in terms of major and minor bleeding events (RE-LY, ROCKET AF, ARISTOTLE, and ENGAGE AF–TIMI 48).[4–7] The RE-LY trial, published by Connolly *et al*.[4] in 2009, was a prospective randomized study comparing the efficacy and safety of dabigatran and warfarin for thromboembolic stroke among patients with AF. In the RE-LY trial, patients were randomized to warfarin and two dabigatran dose (110 and 150 mg b.i.d.) groups. Medication was adjusted in patients using warfarin to maintain a PT/INR of 2.0–3.0. Significantly lower rates of intracranial bleeding were seen with both doses of dabigatran compared to warfarin (both $P < 0.001$). However, increased gastrointestinal bleeding, a major bleeding complication, was found at the high dose of dabigatran, but not at the low dose, compared to warfarin ($P = 0.430$ and $P < 0.001$, respectively).[4] In contrast with the RE-LY trial,[4] our study found no significant differences in the rates of intracranial bleeding between the warfarin-treated patients and 99 NOACs-treated patients, 19 of whom used dabigatran. Consistent with the RE-LY trial,[4] in our study, gastrointestinal bleeding was significantly increased in patients taking NOACs compared to those taking warfarin ($P = 0.021$).

The RE-LY trial revealed significantly lower rates of minor bleeding with both doses of dabigatran compared to warfarin ($P < 0.001$ and $P = 0.005$, respectively). However, mortality rates did not differ significantly between either low- or high-dose dabigatran (110 and 150 mg b.i.d., respectively) and warfarin ($P = 0.130$ and $P = 0.051$, respectively).[4] By contrast, the present study found no significant difference in the rate of minor bleeding between the warfarin-treated and 99 NOAC-treated patients, 19 of whom used dabigatran. Similar to the RE-LY trial,[4] we found no significant difference in mortality between patients using NOACs and those using warfarin ($P = 0.789$).

The ROCKET-AF study, conducted by Patel *et al.*,[5] was a double-blind trial comparing rivaroxaban and dose-adjusted warfarin. The trial revealed no significant between-group difference in the overall rate of major bleeding events (3.6% and 3.4%, respectively; $P = 0.580$). However, gastrointestinal bleeding, a major bleeding event, occurred more frequently in the rivaroxaban group (3.2%) compared to the warfarin group (2.2%) ($P < 0.001$). Additionally, intracranial and fatal bleeding were lower in the rivaroxaban than warfarin group. The ROCKET-AF study reported similar mortality rates for the rivaroxaban and warfarin groups ($P = 0.073$). Similar to Patel *et al.*'s study,[5] the present study identified no significant differences in the rates of major bleeding events or mortality between the warfarin group and 99 NOACs patients, 45 of whom were taking rivaroxaban. Additionally, gastrointestinal bleeding was significantly increased in the NOACs compared to warfarin group. Unlike Patel *et al.*'s study,[5] we found no significant differences in the rates of intracranial bleeding or fatal bleeding complications between the NOACs and warfarin groups.

In the ARISTOTLE study, Granger *et al*.[6] compared apixaban with dose-adjusted warfarin in 18,201 patients with AF. Their results showed no significant difference between the warfarin and NOACs groups in gastrointestinal bleeding ($P = 0.370$), whereas overall minor and major bleeding complications occurred more frequently in the warfarin than apixaban group (all comparisons, $P < 0.001$). Additionally, apixaban was associated with less intracranial bleeding and lower mortality than warfarin ($P < 0.001$ and $P = 0.047$, respectively). In contrast to the ARISTOTLE study,[6] we found no significant differences in overall major and minor bleeding rates between the warfarin-treated patients and 99 NOACs-treated patients, 29 of whom used apixaban. Furthermore, unlike the ARISTOTLE study,[6] no significant difference was found between the NOACs and warfarin groups in the rates of intracranial bleeding or mortality ($P = 0.102$ and $P = 0.789$, respectively).

In a study including 76,940 patients that compared apixaban with warfarin, Li *et al*.[18] found that major bleeding, intracranial bleeding, and gastrointestinal bleeding complications occurred significantly less

frequently with apixaban than warfarin. Finally, unlike Li *et al.*'s[18] study, although the rate of intracranial bleeding, as a major and fatal bleeding complication, was not significantly different between the warfarin and NOAC groups, the rate of gastrointestinal bleeding was significantly higher in the NOAC group.

The ENGAGE AF-TIMI 48 study,[7] the largest clinical trial to date addressing moderate-to-high-risk AF, included 21,105 patients from 46 countries and 1,393 centers. In that study, high-dose edoxaban (60 mg orally once a day) and low-dose edoxaban (30 mg orally once a day) were compared to dose-adjusted warfarin in AF patients. Significantly lower rates of intracranial bleeding were observed under both edoxaban regimens compared to warfarin ($P < 0.001$ for all comparisons). Additionally, gastrointestinal bleeding occurred significantly less frequently under both edoxaban regimens than under warfarin treatment ($P < 0.001$ and $P = 0.030$, respectively). Furthermore, both edoxaban regimens caused significantly fewer major bleeding complications than warfarin ($P < 0.001$ for all comparisons), and minor bleeding complications were significantly less frequent under both edoxaban regimes than with warfarin ($P < 0.001$ and $P = 0.002$; respectively). No statistically significant difference in mortality was observed between high-dose edoxaban and warfarin, whereas the mortality rate for low-dose edoxaban was lower than that for warfarin ($P = 0.080$ and $P = 0.006$, respectively). In contrast to the ENGAGE AF–TIMI 48 study,[7] our study found no significant difference in overall major and minor bleeding rates between the warfarin-treated group and 99 NOACs-treated patients, 6 of whom used edoxaban. In addition, unlike that study, we found no significant differences in the rates of intracranial bleeding or mortality between patients taking NOACs and those taking warfarin ($P = 0.102$). However, gastrointestinal bleeding was significantly increased in the NOACs compared to the warfarin group ($P = 0.021$). Moreover, our study demonstrated that there was no significant difference between warfarin-treated patients and NOACs-treated patients due to AF in the rates of minor bleeding events (47.8% vs. 36.7%, P = 0.153). However, major bleeding events were significantly reduced in patients taking warfarin for AF than those taking NOACs (52.2% vs. 63%, P = 0.008).

According to a study of 186,132 patients conducted by Amin *et al.,*[19] although apixaban- (hazard ratio, 0.510, 95% CI: 0.440–0.580) and dabigatran-treated patients (hazard ratio, 0.790, 95% CI: 0.690–0.910) exhibited significantly fewer major bleeding complications compared to warfarin patients, rivaroxaban-treated patients (hazard ratio, 1.170, 95% CI: 1.100–1.260) showed increased major bleeding complications compared to warfarin-treated patients. Additionally, whereas complications of gastrointestinal bleeding associated with rivaroxaban and apixaban were significantly reduced compared to warfarin, no significant difference was found between dabigatran and warfarin.[19] In contrast to Amin *et al.*'s study,[19] the rates of all major bleeding events in our study did not differ significantly between the warfarin-treated patients and the 99 NOACs-treated patients, including 19 on dabigatran, 45 on rivaroxaban, 29 on apixaban, and 6 on edoxaban, whereas gastrointestinal system bleeding was significantly increased in NOACs-treated compared to warfarin-treated patients.

According to a meta-analysis published by Ruff *et al.,*[20] which included the RE-LY (the main study of dabigatran), ROCKET-AF (main study of rivaroxaban), and ARISTOTLE and ENGAGE AF–TIMI 48 (main studies of edoxaban) trials, NOACs significantly reduced all-cause mortality and intracranial hemorrhage, but increased gastrointestinal bleeding. Consistent with that meta-analysis,[20] in our sample of 99 NOACs-treated patients, NOACs increased gastrointestinal bleeding risk as a major and non-fatal bleeding complication. However, there was no significant decrease in the risk of intracranial bleeding, a major and fatal bleeding event or mortality, in NOACs-treated patients compared to warfarin-treated patients.

A study of 5,254 patients conducted by Jacobs *et al.,*[21] found that the rates of all minor and major bleeding events were significantly lower in the NOACs than the warfarin group. However, no significant difference in mortality was found between the groups. Singer *et al.,*[22] whose study included 437 patients using oral anticoagulants admitted to the ED with bleeding events, reported higher mortality rates in warfarin- than NOACs-treated patients. However, this difference was not statistically significant. In contrast Jacobs *et al.,*[21] the present study found no significant difference in overall major and minor bleeding rates between patients taking NOACs and those taking warfarin. Similar to previous research,[21,22] our study found no significant difference in mortality between patients taking NOACs and those taking warfarin. Additionally, in our multivariate logistic regression analysis, advanced age and male gender remained as independent predictors of mortality in patients with bleeding events due to oral anticoagulants, including both NOACs and warfarin.

In a study of 59 patients (46 warfarin, 13 NOACs) with major bleeding events including intracranial bleeding associated with oral anticoagulant use, Woo *et al.,*[23] reported that patients taking NOACs were significantly older than those taking warfarin ($P = 0.036$). Similarly,

in our study, the mean age was significantly higher in patients with major or minor bleeding who were treated with NOACs compared to those taking warfarin (for all comparisons, $P < 0.001$). There are some limitations to this study, the most important being the small sample size and retrospectively designed from a single center. Besides, data regarding other medications, such as antibiotics, corticosteroids, or antipyretics prescribed to the patients in addition to anticoagulation was lacking, which would be required to evaluate the interaction of those agents with oral anticoagulants on bleeding complications. Thus, a larger perspective, multicenter study involving other drug interactions in patients who presented with bleeding events and were treated with oral anticoagulation is needed to overcome these issues.

Conclusions

Our findings indicate that although the rates of overall major and minor bleeding complications differed among NOACs, the rates of bleeding events were similar to warfarin. Particularly, although gastrointestinal bleeding as a major and relatively non-fatal complication was reduced with warfarin, there was no difference between warfarin and NOACs in terms of intracranial bleeding, a major and fatal bleeding complication. Additionally, major bleeding events were less occurred in AF patients treated with warfarin than those treated with NOACs. We conclude that the use of warfarin by elderly patients is less risky than the use of NOACs in terms of the development of major or minor bleeding complications. In addition, multivariate logistic regression analysis revealed that advanced age and male gender were independent predictors of mortality in patients who developed bleeding events due to either warfarin or NOAC use.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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