Journal of Research in Pharmacy

Research Article

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Multicenter observational study on anticoagulation-related bleeding events in emergency department patients

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Received: 14 August 2024 / Revised: 27 August 2024 / Accepted: 5 September 2024

ABSTRACT: We investigated bleeding complications in patients admitted to the emergency department (ED) who were taking oral anticoagulants and compared the rates of major and minor bleeding events between the direct oral anticoagulant (DOAC) and warfarin groups. We conducted a prospective, multicenter observational study of warfarin- and DOAC-treated patients who presented to the EDs of tertiary-care hospitals between July 2020 and July 2021 with a bleeding event. Among 518 patients on anticoagulation therapy, 121 (23.4%) presented to EDs with bleeding events. A chart review revealed 73 (60.24%) patients with bleeding events who were taking a DOAC (i.e., apixaban, edoxaban, rivaroxaban, or dabigatran) and 48 who were taking warfarin. The rate of bleeding events was significantly higher among patients treated with warfarin than among those treated with DOACs (48/129 [37.2%] vs. 73/389 [18.8%], p<0,001). Subgroup analysis of the DOAC-treated patients revealed a significant difference in the frequency of bleeding events among the DOAC groups (p=0.016), with a significantly lower frequency in patients treated with rivaroxaban versus edoxaban (14.9% vs. 34.7%, p=0.002) and in those treated with apixaban versus edoxaban (18.8% vs. 34.7%, p=0.021). Our findings indicate that although the rates of overall bleeding events differed among DOAC-treated patients, the rates of bleeding events were lower than those in warfarin-treated patients. Additionally, major bleeding events occurred less frequently in patients treated with rivaroxaban or apixaban compared with edoxaban

KEYWORDS: Oral anticoagulants; bleeding events; direct oral anticoagulant; warfarin

1. INTRODUCTION

Direct oral anticoagulants (DOACs) offer several advantages over vitamin K antagonists (VKAs), including enhanced patient adherence, the elimination of the need for dose adjustments or regular prothrombin time/international normalized ratio (INR) monitoring, reduced risk of intracranial hemorrhage, and a lower probability of drug interactions [1-4]. Although DOACs are associated with an increased risk of gastrointestinal bleeding, this is offset by a decreased incidence of major and fatal bleeding events compared to VKAs [5].

It is important to note that there is a lack of direct comparative studies on DOACs, and limited data are available concerning the overall characteristics of patients receiving oral anticoagulants who present to the emergency department (ED), regardless of their reason for admission [6]. To address these gaps, we conducted a prospective, year-long study of all ED-admitted patients on oral therapeutic anticoagulation therapy, aiming to evaluate their indications for use and to assess bleeding complications.

2. RESULTS

During the study period from July 1, 2020, to July 1, 2021, a total of 518 patients were admitted to the emergency department (ED) while on oral therapeutic anticoagulation therapy. Of these, 129 patients (24.9%) were on warfarin, whereas 389 patients (75.1%) were on direct oral anticoagulants (DOACs). Within the DOAC cohort, 149 patients (38.3%) were receiving apixaban, 49 (12.6%) were on edoxaban, 17 (4.4%)

How to cite this article: Cakmak S, Sogut O, Ilhan B, Simsekoğlu R, Umit TB, Doğan H, Unlıkaplan IM . Multicenter observational study on anticoagulation-related bleeding events in emergency department patients. J Res Pharm. 2024; 28(6): 2243-2250.

ISSN: 2630-6344

http://dx.doi.org/10.29228/jrp.898

were on dabigatran, and 174 (44.7%) were on rivaroxaban. Among the 121 patients who experienced bleeding, 23 (19%) died within the first 30 days of hospital admission while on oral anticoagulant therapy. Of these 23 deaths, 40.6% (9 patients) occurred in the warfarin group, compared to 59.4% (14 patients) in the DOAC group (p = 0.897).

Regarding bleeding complications and outcomes, 121 patients (23.4%) presented to the ED with bleeding while on anticoagulation therapy. The bleeding incidence was significantly higher in the warfarin group than in the DOAC group (p < 0.001). A notable difference in bleeding rates was also observed among the different DOACs (p = 0.016); specifically, patients on edoxaban had a significantly higher bleeding rate compared to those on apixaban and rivaroxaban (p = 0.021 and p = 0.002, respectively). However, no significant difference in bleeding rates was found between the edoxaban and warfarin groups (p = 0.756; Table 1)

Table 1a. Bleeding events according to anticoagulant type

Anticoagulant type	**Bleeding events**		
	n	%	p
Warfarin	48	37.2	
Direct oral anticoagulant	73	18.8	<0.001
Apixaban	28	18.8	
Edoxaban	17	34.7	0.016
Dabigatran	2	11.8	
Rivaroxaban	26	14.9	

* Intergroup analyses (warfarin vs. DOACs) were conducted using chi-squared test.

Table 1.b Subgroup analysis

		p
Direct oral anticoagulant	Edoxaban vs. Apixaban	0.021
	Edoxaban vs. Dabigatran	0.119
	Edoxaban vs. Rivaroxaban	0.002
	Apixaban vs. Dabigatran	0.740
	Apixaban vs. Rivaroxaban	0.355
	Dabigatran vs. Rivaroxaban	>0.99
	Edoxaban vs. Warfarin	0.756

There were no significant difference in bleeding type (major/minor) between the warfarin and DOAC groups (p = 0.207 and p = 0.920, respectively; Table 2). However, a noteworthy finding was that a higher number of patients experiencing bleeding were on DOACs compared to those on warfarin, specifically in cases related to AF (atrial fibrillation) and MVR (mechanical valve replacement) (p < 0.001; Table 2). The mean serum INR and APTT were notably elevated in patients with warfarin-associated bleeding compared to those with DOAC-related bleeding (both p < 0.01; Table 2). Notably, within the subset of patients on oral anticoagulants, those prescribed DOACs were significantly older than those prescribed warfarin (p < 0.001). Moreover, among patients experiencing bleeding, those on DOACs were also significantly older than their warfarin counterparts (p = 0.024; Table 2).

Using the enter method in multivariate logistic regression analysis, advanced age was identified as an independent predictor of mortality (odds ratio [OR]: 1.054; 95% confidence interval [CI]: 1.002–1.108; p = 0.041) in patients experiencing bleeding complications related to oral anticoagulant therapy (Table 3). Additionally, the backward selection method revealed chronic renal failure (CRF) as an independent predictor of mortality in this patient cohort (OR: 4.926; 95% CI: 1.454–16.686; p = 0.010; Table 3).

Table 2. Demographic characteristics, indications, comorbidities, laboratory findings, and outcomes according to the anticoagulant type in patients with bleeding events

Characteristic	Warfarin n (%)	Direct oral anticoagulant n (%)	p
Major Bleeding types			
Gastrointestinal Bleeding	13 (27.1%)	29 (39,7%)	0.153
Intracranial Bleeding	7 (14.6%)	11 (15.1%)	0.942
Rectus Sheath Hematoma	1 (2.1%)	0 (0.0%)	0.397
Alveolar Bleeding	1 (2.1%)	0 (0.0%)	0.397
Vaginal Bleeding	0 (0,0%)	2 (2.7%)	0.517
Minor Bleeding types			
Ecchymosis	1 (2.1%)	5 (6.8%)	0.401
Epistaxis	1 (2.1%)	1 (1.4%)	<0.99
Hematuria	16 (33.3%)	20 (27.4%)	0.485
Hematoma	1 (2.1%)	1 (1.4%)	<0.99
Gingival Bleeding	5 (10.4%)	3 (4.1%)	0.262
Subconjunctival hemorrhage	2 (4.2%)	1 (1.4%)	0.562
Comorbidities			
Atrial fibrillation	26 (54.2%)	63 (86.3%)	<0.001
Stroke	14 (29.2%)	13 (17.8%)	0.142
Venous thromboembolism	6 (12.5%)	4 (5.5%)	0.192
Mechanical valve replacement	14 (29.2%)	0 (0.0%)	<0.001
Coronary artery disease	21 (43.8%)	31 (42.5%)	0.889
Chronic renal failure	5 (10.4%)	15 (20.5%)	0.142
Chronic liver disease	0 (0.0%)	0 (0.0%)	-
Hypertension	29 (60.4%)	54 (74.0%)	0.116
Chronic heart failure	17 (35.4%)	31 (42.5%)	0.438
Diabetes mellitus	13 (27.1%)	22 (30.1%)	0.717
Indications for anticoagulant therapy			
Atrial fibrillation	26 (54.2%)	63 (86.3%)	<0.001
Stroke	12 (25.0%)	12 (16.4%)	0.248
Mechanical valve replacement	14 (29.2%)	0 (0.0%)	<0.001
Venous thromboembolism	6 (12.5%)	4 (5.5%)	0.192
Laboratory findings			
Hemoglobin (g/dL)	9.8 (9.7-9.9)	9.8 (9.5-9.9)	0.107
Platelet (10^3/µL)	122 (115-136)	122.50 (106-134)	0.149
International normalized ratio (seconds)	2.19 (1.85-2.62)	2.37 (1.91-2.90)	<0.001
Activated partial thromboplastin time (seconds)	16 (12.30-20.45)	12.10 (10.27-15.52)	<0.001
Creatinine (mg/dL)	3.22 (2.69-3.92)	2.99 (2.49-3.57)	0.045

Outcome	Discharged	9 (18.8%)	24 (32.9%)	0.173
n (%)	Hospitalization	30 (62.4%)	32 (43.8%)	
	Intensive care unit	9 (18.8%)	17 (23.3%)	
Mortality	Survivor	35 (72.9%)	54 (74.0%)	0.955
	Died with in 30 days	9 (18.8%)	14 (19.2%)	
	Died after 30 days	4 (8.3%)	5 (6.8%)	

Data are expressed as numbers (n), percentages (%), median and interquartile range (IQR).

Intergroup Subgroup analyses (warfarin vs. DOACs) were conducted using chi-squared and Mann–Whitney U tests, as appropriate.

Table 3. Multivariate logistic regression analysis utilizing both the enter and backward methods identified independent predictors of mortality

		p	OR	95% CI	
Enter Method	Age (years)	0.041	1.054	1.002	1.108
	Gender (Ref:female) male	0.751	1.177	0.430	3.226
	Coronary artery disease	0.111	2.268	0.828	6.210
	Hypertension	0.047	0.318	0.103	0.984
	Diabetes mellitus	0.967	1.024	0.336	3.116
	Chronic renal failure	0.053	4.427	0.982	19.962
	Hemoglobin	0.311	1.099	0.916	1.318
	Platelet	0.732	1.001	0.996	1.006
	Creatinin	0.230	1.357	0.824	2.232
	International normalized ratio	0.373	0.870	0.641	1.181
	Activated partial thromboplastin time	0.644	1.008	0.974	1.043
	Ref: Warfarin	0.152			
	Apixaban	0.052	0.214	0.045	1.012
	Edoxaban	0.386	0.511	0.112	2.334
	Dabigatran	0.999	0.000	0.000	.
	Rivaroxaban	0.599	1.411	0.391	5.092
Backward Method	Age (years)	0.062	1.044	0.998	1.092
	Coronary artery disease	0.090	2.264	0.881	5.817
	Hypertension	0.017	0.279	0.098	0.796
	Chronic renal failure	0.010	4.926	1.454	16.686
	Ref:Warfarin	0.194			
	Apixaban	0.099	0.302	0.073	1.254
	Edoxaban	0.642	0.719	0.179	2.893
	Dabigatran	0.999	0.000	0.000	.
	Rivaroxaban	0.265	1.863	0.624	5.561

Abbreviations: OR, odds ratio; CI, confidence interval;

3. DISCUSSION

Among the 518 patients on anticoagulation, 121 (23.4%) presented to the ED with a bleeding event. The incidince of bleeding events was significantly higher among patients treated with warfarin versus DOACs (37.2% vs. 18.8%, $p < 0.001$). Subgroup analysis within the DOAC group revealed a significant difference in the frequency of bleeding events among the different DOACs, with lower frequencies among those taking rivaroxaban versus edoxaban (14.9% vs. 34.7%, $p = 0.002$) and those taking apixaban versus dabigatran (18.8% vs. 34.7%, $p = 0.021$). In this study, a significant age difference was observed among patients on oral anticoagulants, with those receiving direct oral anticoagulants (DOACs) being significantly older than those on warfarin ($p < 0.001$). This age difference was also apparent among patients who experienced bleeding events, with DOAC users being notably older than warfarin users ($p = 0.024$). Moreover, a significantly greater proportion of patients using oral anticoagulants for atrial fibrillation (AF), mechanical valve replacement (MVR), and venous thromboembolism (VTE) were on DOACs compared to warfarin ($p < 0.001$, $p < 0.001$, and $p = 0.022$, respectively). Multivariate logistic regression analysis, employing the enter method, identified advanced age as an independent predictor of mortality in patients with bleeding complications associated with oral anticoagulant use (odds ratio [OR]: 1.054; 95% confidence interval [CI]: 1.002–1.108; $p = 0.041$). Additionally, chronic renal failure (CRF) was found to be an independent predictor of mortality using the backward selection method in this patient group (OR: 4.926; 95% CI: 1.454–16.686; $p = 0.010$).

Several randomized, double-blind multicenter studies, including ARISTOTLE, ENGAGE AF–TIMI 48, RE-LY and ROCKET-AF, have compared DOACs with warfarin, focusing on major and minor bleeding events [9-12]. A meta-analysis of these studies, encompassing 71,683 patients and conducted by Antony et al. (2022), found that DOACs significantly reduced the risk of intracranial hemorrhage. However, there was no significant decrease in the risk of major bleeding events in DOAC-treated patients compared with those treated with warfarin. Aligning with this meta-analysis, our study, involving 73 DOAC-treated patients, revealed an increased incidince of bleeding events with DOACs. Nonetheless, no significant reduction in the risk of mortality or intracranial bleeding—considered a major bleeding event—was observed in DOAC-treated patients compared to warfarin-treated patients [7]. However, a recent meta-analysis conducted in 2021, the mortality rates associated with bleeding events attributed to DOACs were observed to surpass those linked to warfarin therapy. [13]

In the RE-SPECT CVT study [14], dabigatran (150 mg twice daily) undergone comparison with dose-adjusted warfarin in patients with cerebral venous thrombosis (CVT). No significant disparity in bleeding events emerged between individuals receiving dabigatran and those receiving warfarin. Conversely, in the ACTION-CVT study, Yaghi et al. evaluated the efficacy of DOACs compared to warfarin in a real-world CVT cohort. Their extensive multicenter, international, retrospective investigation, spanning 845 patients across 27 centers, revealed a markedly lower incidence of bleeding events in the DOAC group compared to the warfarin group [15]. Similarly, our study unveiled a significantly diminished bleeding rate in the DOAC group compared to the warfarin group. Woo et al. [16] also noted a notable finding regarding the mean age of patients experiencing major bleeding events, which was significantly higher in those treated with DOACs versus warfarin, mirroring our study findings. Moreover, a meta-analysis by Mitchell et al. [17] scrutinizing DOAC and warfarin usage among individuals aged 75 years or older with AF yielded no significant discrepancies in major bleeding or mortality rates between DOAC and warfarin users. In contrast, our study found a significantly higher bleeding rate in the warfarin group compared to the DOAC group, contrary to the findings of Mitchell et al.'s meta-analysis. Lawal et al.'s investigation involving 10,200 patients [8] found a significantly higher risk of major bleeding for rivaroxaban users compared to apixaban users. In contrast, our present study did not reveal any notable difference in major bleeding rates between patients on rivaroxaban and those on apixaban. However, a distinctive finding in our study was the significantly lower occurrence of major bleeding complications among patients using apixaban or rivaroxaban compared to those using edoxaban, which may be due to the smaller sample size. In another study by Amin et al. [18], the rate of major bleeding events was significantly reduced in patients taking dabigatran or apixaban compared to warfarin, while rivaroxaban-treated patients had a higher risk of major bleeding events compared to warfarin-treated patients. Additionally, although apixaban- and rivaroxaban-treated patients experienced significantly fewer gastrointestinal bleeding complications compared to warfarin-treated patients, no significant difference was observed between dabigatran- and warfarin-treated patients. Contrary to Amin et al.'s findings, our study did not identify any significant differences in the rates of overall major or minor bleeding events between patients on DOACs and those on warfarin. Consistent with findings from prior

investigations [17,19,20], our study revealed no significant disparity in mortality rates between individuals utilizing DOACs and those employing warfarin. Despite an increased incidence of bleeding events among warfarin users, the absence of a mortality discrepancy may be due to the higher average age of patients using DOACs. Furthermore, our multivariate logistic regression analysis underscored that advanced age independently predicted mortality in patients experiencing bleeding events related to oral anticoagulant use, encompassing both DOACs and warfarin. Employing the backward method, we identified that CRF, as a comorbidity, retained its status as an independent predictor of mortality in patients grappling with bleeding complications associated with oral anticoagulant use.

Study Limitations

This study has several limitations. First, the study was conducted in tertiary-care hospitals in a single country, potentially limiting the generalizability of the findings to other healthcare settings or regions. Second, the focus on patients presenting to the emergency department may introduce selection bias, as it does not account for bleeding events managed in other settings or those that do not require emergency care. Nevertheless, our study has notable strengths; all data for this study were collected prospectively. The data recording by expert physicians in the tertiary hospital were performed by the same staff, eliminating the possibility of bias.

4. CONCLUSION

In summary, the findings from this study indicate that the incidence of bleeding events varied across different DOACs with a general trend of lower rates in DOAC-treated patients compared to those treated with warfarin. Notably, major bleeding events were less frequent in patients receiving rivaroxaban or apixaban when compared to those on edoxaban.

5. MATERIALS AND METHODS

5.1. Ethics Committee Approval

The research employed a prospective, multicenter design in accordance with the principles outlined in the 1989 Declaration of Helsinki. The study was approved by the Local Ethics Committee of Istanbul Bakirkoy Dr. Sadi Konuk Research and Training Hospital (number: 2020/97).

5.2. Study Design and Setting

We performed a prospective observational study of VKA (warfarin)- and DOAC-treated nontraumatic patients aged 18 years or older between 1 July 2020 and 1 July 2021.

Three patients with bleeding events who were using warfarin were excluded from the study because their PT/INR was < 1.5. Twenty-seven 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. Six other patients were excluded because they had a history of trauma.

Finally, 518 patients undergoing oral therapeutic anticoagulation therapy (warfarin or DOACs) at admission to the ED were included in the study. Among 518 patients on anticoagulation therapy, 121 (23.4%) presented to EDs with bleeding.

We determined that 22 patients had major, and 26 minor, bleeding associated with warfarin use, while 42 patients had major, and 31 patients minor, bleeding associated with DOACs use. Each patient underwent a comprehensive chart review, assessing clinical characteristics and bleeding complications. Evaluation included patient demographics, type and indications for anticoagulation, comorbidities, and laboratory results, such as hemoglobin level, platelet count, serum creatinine level, INR, and activated partial thromboplastin time (APTT). Major bleeding events were defined by occurrences such as gastrointestinal, retroperitoneal, alveolar, vaginal, cranial, and intra-abdominal bleeding, or a 2-unit decline in hemoglobin levels necessitating a transfusion of more than 3 units of packed red blood cells. Clinically significant minor bleeding was identified by criteria including skin ecchymosis, skin hematomas exceeding 25 cm^2, spontaneous epistaxis lasting over 5 minutes, and gingival bleeding persisting for more than 5 minutes. Comparison parameters between patients experiencing major and minor bleeding complications encompassed age, sex, comorbidities, indications for anticoagulant therapy, laboratory results, anticoagulant type, and bleeding site. Additionally, the study examined 30-day mortality rates associated with life-threatening major bleeding events in individuals prescribed DOACs and warfarin.

The required sample size was calculated by power analysis before data collection based on information from previous studies [4,7,8]. An estimated 447 patients on anticoagulation therapy and 72 patients who had bleeding events while taking warfarin or DOACs were required to detect significant differences between the groups with a power of 95% and an alpha error of 5%. Statistical analyses were conducted using SPSS 21.0 for Windows.

5.3. Statistical Analysis

The presentation of numerical data involves means ± standard deviation or medians accompanied by the range. Categorical variables, such as sex and age, are conveyed through numerical counts (n) and corresponding percentages (%). For normally distributed data within groups, the chi-square test was employed, while the Mann–Whitney U-test with Bonferroni correction was applied for non-normally distributed data. The non normality was observed by performing Shappiro Wilk test. Multivariate logistic regression analysis was utilized to examine independent variables. Statistical significance was acknowledged for a p-value < 0.05.

Acknowledgements: None
Author contributions : Concept – S.Ç.,Ö.S.; Design – S.Ç., Ö.S.; Supervision – S.Ç.,Ö.S., H.D., B.İ.,; Resources – S.Ç., R.Ş., T.B.Ü., I.M.Ü.,; Materials – S.Ç., R.Ş., T.B.Ü., I.M.Ü.; Data Collection and/or Processing – S.Ç., R.Ş., T.B.Ü., I.M.Ü.; Analysis and/or Interpretation – S.Ç., R.Ş., Ö.S.; Literature Search – S.Ç., R.Ş., T.B.Ü., I.M.Ü.; Writing – S.Ç., Ö.S.; Critical Reviews – all autors.
Conflict of interest statement: Authors declared no conflict of interest.
Funding Disclosure: The authors affirm that no financial backing was received for the research, authorship, and/or publication of this study.

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