Bleeding associated with new oral anticoagulants: a retrospective study

Zeyad G. Alharbi [1], Eman A. Balahmar [2], Sultan M. Allihybi [1], Anas T. Katib [1], Kalil M. Alkishan [1], Ammar M. Bahati [1], Mohammed Babakkor [3]

(1) Faculty of Medicine, Umm Alqura University, Makkah, Saudi Arabia.
(2) Faculty of Pharmacy, Imam Abdulrahman Bin Faisal University, Dammam, Saudi Arabia.
(3) Department of neurology. King Abdullah Medical City, Makkah, Saudi Arabia

Corresponding author:
Dr. Sultan M. Allihybi
Saudi Arabia
Phone: +966562699560
Email: Allehybi.sultan@gmail.com

Received: November 2022 Accepted: December 2022; Published: December 30, 2022.
Citation: Zeyad G. Alharbi et al. Bleeding associated with new oral anticoagulants: a retrospective study. World Family Medicine. December 2022 - January 2023 Part 2; 21(1):77-85 DOI: 10.5742/MEWFM.2023.95251564

Abstract

Background: Stroke and systemic embolic occurrences have been significantly reduced by novel oral anticoagulants, though theoretically a side effect of this anticoagulant treatment is hemorrhagic stroke.

Objectives: to determine bleeding associated with new oral anticoagulants in King Abdullah Medical City (KAMC), Makkah, Saudi Arabia.

Methods: A retrospective study was done at King Abdullah Medical City (KAMC), Makkah, Saudi Arabia on patients who used NOAC between January 2013 to June 2019. Data about patients' demographics, comorbidities, clinical data, NOAC used and subsequent bleeding complications, and antiplatelets use, were collected.

Results: This study found that atrial fibrillation (AF) was the most common reason NOACs like Edoxaban and Rivaroxaban were administered. About 71% of patients received antiplatelet therapy, with aspirin and stains being the most popular options. 1.2% of the patients with GIT bleeding, 1.2% with UGIB, and 2.4% with LGIB experienced cerebral haemorrhage following NOAC treatment. However, patients who experienced GIT haemorrhage after taking a NOAC were much more likely to have a history of UGIB or LCIB and to have taken Edoxaban as a NOAC.

Conclusion: To demonstrate the safety, efficacy, and effectiveness of NOACs, future multi-center studies with a larger sample size should be conducted.

Keywords: bleeding, associated, NOACs, retrospective, KAMC

Introduction

In various therapeutic circumstances, oral anticoagulant (OAC) medicines are used to prevent thromboembolic consequences (1). Vitamin K antagonists (VKA) were the sole class of OAC used up until the past ten years (2). They are primarily utilised in the treatment of cardiogenic shock, prosthetic heart valve dysfunction, pulmonary embolism, and atrial fibrillation (AF) (3). Although they can help prevent thromboembolic illnesses, they also carry a risk of several side effects, such as intracranial haemorrhage (ICH) and gastrointestinal bleeding (GIB) (4).

Oral anticoagulants associated intracerebral haemorrhage (OAC-ICH) incidence has climbed to 15% in the general population and up to 24% in tertiary care facilities during the past few years, as the prevalence of AF increased to (1%–2%) of the general population (4,5). OAC-ICH has a 7–10-fold higher mortality rate than spontaneous ICH, despite the fact that both conditions share the same risk factors, such as advanced age, hypertension, and a history of ischemic stroke (6).

Due to its extremely dismal prognosis and despite newer, more aggressive therapy options, ICH is the most dreaded consequence (7). GIB, a frequent emergent condition, is another serious consequence. With a mortality rate of 5–10% and an annual hospital admission rate of 150 per 100,000 of the overall population (7). GI bleeding is seen as a life-threatening condition that requires aggressive therapy, yet many instances can mostly be treated in an outpatient setting (8).

Among other medications that were shown to be closely connected with GIB, such as nonsteroidal anti-inflammatory medicines (NSAIDs), low dose aspirin, and antiplatelet agents, anticoagulants have been revealed to have the highest risk of GIB (9). VKA was highly effective at preventing thromboembolism despite this. They have a limited therapeutic range, a high risk of bleeding, frequent monitoring, and dose modifications, all of which add up to significant danger and discomfort (10).

A novel class of oral anticoagulants known as NOACs has recently been created (dabigatran etexilate, varoxaban, apixaban, edoxaban, betrixaban eribaxaban). They are superior to VKA, which has reduced the rate of ICH by 40–70%, in several ways (11). Patients taking new oral anticoagulants saw a significant decrease in stroke and systemic embolic events. This advantage was primarily caused by a significant reduction in haemorrhagic stroke risk, which was cut in half. Haemorrhagic stroke is conceptually a side effect of anticoagulant therapy even though it is measured as part of the total efficacy of these medications (12).

The anticoagulant impact of NOACs is substantially shorter than that of VKAs, with the beginning of anticoagulation occurring 1 to 4 hours after initial dose (13). Contrary to VKAs, the anticoagulant action does not require monitoring, and dose modifications are typically not required. Although NOAC-specific antidotes are undergoing preclinical and clinical testing, they have not yet been made widely accessible (13.14). Compared to individuals who are not taking anticoagulants, it is currently unknown if NOACs raise the risk of subsequent hematoma enlargement in ICH (14).

Apixaban, dabigatran, and rivaroxaban are three new oral anticoagulants (NOACs) that have had inconsistent outcomes. Dabigatran 150mg reduces risk of stroke with similar bleeding risk, but slightly increases risk of gastrointestinal bleeding and myocardial infarction; rivaroxaban may be as effective as warfarin in preventing stroke or systemic embolism. Apixaban reduces risk of stroke without increasing risk of major bleeding or intracranial haemorrhage (14,15).

Although the effect of NOAC on gastrointestinal bleeding is still unknown, strong evidence for a higher risk may be drawn from an analysis of the most recent data from phase II/III studies involving more than 150,000 patients (16). GI haemorrhage increases by 30% when NOAC is used in comparison to normal anticoagulant medication, on top of a 2- to 3-fold increase in GI bleeding risk when NOAC is not used (9). Anticoagulants are required for all patients due to the recent rise in the number of Atrial Fibrillation patients who have received a new diagnosis. The determination of the risk associated with the use of new oral anticoagulants could help in using them in a more proficient manner that would reduce the risk of thromboembolism to patients without the risk of bleeding (17).

This retrospective study aimed to assess bleeding associated with new oral anticoagulants in King Abdullah Medical City (KAMC), Makkah, Saudi Arabia.

Subjects and Methods

Study design, location and time: This was a retrospective study done at King Abdullah Medical City (KAMC), Makkah, Saudi Arabia from May to August 2022.

Study population: the study participants were all cases that used NOAC between January 2013 to June 2019.
Data collection: a pre-designed checklist was prepared to collect data from patients' medical records. Data collected included patients' demographics, comorbidities, clinical data, NOAC used and subsequent bleeding complications and antiplatelets use.

Ethical considerations: ethical approval for the study was obtained from KAMC Institutional review board (IRB) (No: 18-484).

Data analysis: data were analyzed using the (SPSS) program version 26. To assess the relationship between variables, qualitative data was expressed as numbers and percentages, and the Chi-squared test ($\chi 2$) was used. Quantitative data was expressed as mean and standard deviation (Mean ± SD), and non-parametric variables were tested using the Mann-Whitney test. A p-value < 0.05 was considered statistically significant.

Results

(Table 1) shows that the mean age of studied patients was 62.73 ± 15.09 years and 52.4% were females. Of them, 9.1% were smokers, 79.8% were hypertensive, 0.7% were drug abusers and 0.3% were alcohol abusers. Only 0.9% had bleeding disorders and 3.6% had vascular diseases. Only 5.7% had previous history of bleeding, 0.9% had a history of ICH and 1% had a history of UGIB or LGIB. Of them, 8.3% had chronic diseases with heart diseases the most common (59.5%).

Table 1. Distribution of studied patients according to their demographic and clinical data (No.: 580)

Variable	No. (%)
Age	62.73 ±15.09
Gender	
Female	304 (52.4)
Male	276 (47.6)
Smoking	
Yes	53 (9.1)
No	527 (90.9)
HTN	
Yes	463 (79.8)
No	117 (20.2)
Drug abuse	
Yes	4 (0.7)
No	576 (99.3)
Alcohol abuse	
Yes	2 (0.3)
No	578 (99.7)
Bleeding disorder	
Yes	5 (0.9)
No	575 (99.1)
Vascular disease	
Yes	21 (3.6)
No	559 (96.4)
Previous history of bleeding	
Yes	33 (5.7)
No	546 (94.3)
Previous history of ICH	5 (0.9)
Previous history of UGIB	6 (1)
Previous history of LGIB	6 (1)
Chronic diseases	
Yes	48 (8.3)
No	532 (91.7)
If yes, specify:	
Heart disease	345 (59.5)
Renal disease	87 (15)
Liver disease	15 (2.6)

Table 2. Distribution of studied patients according to pattern of NOAC used and subsequent bleeding complications and antiplatelets use (No.: 580)

Table 2. Distribution of studied patients according to pattern of NOAC used and subsequent bleeding complications and antiplatelets use (No.: 580)

Variable	No. (%)
NOAC used	
Dabigatran	82 (14.1)
Apixaban	179 (30.9)
Edoxaban	448 (77.2)
Rivaroxaban	316 (54.5)
Reason for using NOAC	
AF	409 (70.5)
Ischemic heart diseases	146 (25.2)
DVT, PE	93 (16)
Other	78 (13.4)
Antiplatelets use	
Yes	415 (71.6)
No	165 (28.4)
If yes, specify:	
aspirin	399 (68.8)
Clopedigril	213 (36.7)
Statins	373 (64.4)
Other medications: NSAIDs	111 (19.1)
Cerebral hemorrhage after using NOAC	
Yes	6 (1)
No	547 (99)
GIT bleeding after using NOAC	
Yes	19 (3.3)
No	561 (96.7)
If yes, specify:	
UGIB	7 (1.2)
LGIB	14 (2.4)
Other bleeding after using NOAC	
Yes	7 (1.2)
No	573 (98.8)
if yes, specify:	
epistaxis	4 (0.7)
vaginal bleeding	4 (0.7)

A non-significant relationship was found between occurrence of cerebral hemorrhage after NOAC use and participants' demographics, clinical data or NOAC usage pattern or antiplatelets use (p=>0.05) (Tables 3 and 4). While patients who had GIT hemorrhage after NOAC use had a significant higher percentage of those having a previous history of UGIB or LCIB (p=<0.05) (Table 5).

Table 3. Relationship between occurrence of cerebral hemorrhage after NOAC use and participants' demographic and clinical data (No.: 580)

Variable	Cerebral hemorrhage after using NOAC		χ2	p-value
	Yes No. (%)	No No. (%)		
Age	62 ±14.39	62.73 ±15.11	0.07*	0.941
Gender				
Female	3 (50)	301 (52.4)	0.01	0.905
Male	3 (50)	273 (47.6)		
Smoking				
Yes	0 (0.0)	53 (9.2)	0.61	0.435
No	6 (100)	521 (90.8)		
HTN				
Yes	4 (66.7)	459 (80)	0.64	0.419
No	2 (33.3)	115 (20)		
Drug abuse				
Yes	0 (0.0)	4 (0.7)	0.04	0.837
No	6 (100)	570 (99.3)		
Alcohol abuse				
Yes	0 (0.0)	2 (0.3)	0.02	0.885
No	6 (100)	572 (99.7)		
Bleeding disorder				
Yes	0 (0.0)	5 (0.9)	0.05	0.818
No	6 (100)	569 (99.1)		
Vascular disease				
Yes	1 (16.7)	20 (3.5)	2.95	0.086
No	5 (83.3)	554 (96.5)		
Previous history of bleeding				
Yes	0 (0.0)	33 (5.7)	0.36	0.545
No	6 (100)	541 (94.3)		
Previous history of ICH				
Yes	0 (0.0)	5 (0.9)	0.05	0.818
No	6 (100)	569 (99.1)		
Previous history of UGIB				
Yes	0 (0.0)	6 (1)	0.06	0.801
No	6 (100)	568 (99)		
Previous history of LGIB				
Yes	0 (0.0)	6 (1)	0.06	0.801
No	6 (100)	568 (99)		
Chronic diseases				
Yes	0 (0.0)	48 (8.4)	0.54	0.46
No	6 (100)	526 (91.6)		
If yes, specify:				
Heart disease	4 (66.7)	341 (59.4)	0.13	0.719
Renal disease	2 (33.3)	85 (14.8)	1.59	0.206
Liver disease	0 (0.0)	15 (2.6)	0.16	0.688

N.B.: * = Mann-Whitney test

Table 4. Relationship between occurrence of cerebral hemorrhage after NOAC use and its usage pattern and antiplatelets use (No.: 580)

Variable	Cerebral hemorrhage after using NOAC		χ2	p-value
	Yes No. (%)	No No. (%)		
NOAC used				
Dabigatran	1 (16.7)	81 (14.1)	0.03	0.858
Apixaban	1 (16.7)	178 (31)	0.57	0.449
Edoxaban	4 (66.7)	444 (77.4)	0.38	0.535
Rivaroxaban	4 (66.7)	312 (54.4)	0.36	0.547
Reason for using NOAC				
AF	5 (83.3)	404 (70.4)	0.47	0.489
Ischemic heart diseases	1 (16.7)	145 (25.3)	0.23	0.629
DVT, PE	2 (33.3)	91 (15.9)	1.34	0.246
Antiplatelets use				
Yes	5 (33.3)	410 (71.4)	0.41	0.52
No	1 (16.7)	164 (28.6)		
If yes, specify:				
aspirin	5 (83.3)	394 (68.6)	0.59	0.44
Clopedigril	3 (50)	210 (36.6)	0.46	0.498
Statins	4 (66.7)	369 (64.4)	0.01	0.908
Other medications: NSAIDS	3 (50)	108 (18.8)	3.73	0.053

Table 5. Relationship between occurrence of GIT hemorrhage after NOAC use and participants' demographic and clinical data (No.: 580)

Variable	GIT hemorrhage after using NOAC		χ^2	p-value
	Yes No. (%)	No No. (%)		
Age	68.56 ±14.89	62.53 ±15.07	1.87*	0.06
Gender				
Female	13 (68.4)	291 (51.9)	2.01	0.155
Male	6 (31.6)	270 (48.1)		
Smoking				
Yes	1 (5.3)	52 (9.3)	0.35	0.551
No	18 (94.7)	509 (90.7)		
HTN				
Yes	17 (89.5)	446 (79.5)	1.13	0.287
No	2 (10.5)	115 (20.5)		
Drug abuse				
Yes	0 (0.0)	4 (0.7)	0.13	0.712
No	19 (100)	557 (99.3)		
Alcohol abuse				
Yes	0 (0.0)	2 (0.4)	0.06	0.794
No	19 (100)	559 (99.6)		
Bleeding disorder				
Yes	0 (0.0)	5 (0.9)	0.17	0.679
No	19 (100)	556 (99.1)		
Vascular disease				
Yes	0 (0.0)	21 (3.7)	0.73	0.39
No	19 (100)	540 (96.3)		
Previous history of bleeding				
Yes	5 (26.3)	28 (5)	15.57	**<0.001**
No	14 (73.7)	533 (95)		
Previous history of ICH				
Yes	0 (0.0)	5 (0.9)	0.17	0.679
No	19 (100)	556 (99.1)		
Previous history of UGIB				
Yes	2 (10.5)	4 (0.7)	17.28	**<0.001**
No	17 (89.5)	557 (99.3)		
Previous history of LGIB				
Yes	2 (10.5)	4 (0.7)	17.28	**<0.001**
No	17 (89.5)	557 (99.3)		
Chronic diseases				
Yes	1 (5.3)	47 (8.4)	0.23	0.628
No	18 (94.7)	514 (91.6)		
If yes, specify:				
Heart disease	14 (73.7)	331 (59)	1.64	0.2
Renal disease	3 (15.8)	84 (15)	0.01	0.922
Liver disease	1 (5.3)	14 (2.5)	0.55	0.455

N.B.: * = Mann-Whitney test

At the same time, while patients who had GIT hemorrhage after NOAC use a significant higher percentage of those received Edoxaban as NOAC and had no DVT or PE (p=<0.05) (Table 6).

Table 6. Relationship between occurrence of GIT hemorrhage after NOAC use and its usage pattern and antiplatelets use (No.: 580)

Variable	GIT hemorrhage after using NOAC		χ2	p-value
	Yes No. (%)	No No. (%)		
NOAC used				
Dabigatran	3 (15.8)	79 (14.1)	**0.04**	0.834
Apixaban	4 (21.1)	175 (31.2)	0.88	0.347
Edoxaban	13 (68.4)	435 (77.5)	0.86	0.351
Rivaroxaban	12 (63.2)	304 (54.2)	0.59	0.44
Reason for using NOAC				
	15 (78.9)	394 (70.2)	0.67	0.413
AF	6 (31.6)	140 (25)	0.42	0.513
Ischemic heart diseases	3 (15.8)	90 (16)	**0.001**	0.976
DVT, PE				
Antiplatelets use				
Yes	16 (84.2)	399 (71.1)	1.54	0.214
No	3 (15.8)	162 (28.9)		
If yes, specify:				
aspirin	14 (73.7)	385 (68.6)	0.21	0.64
Clopedigril	6 (31.6)	207 (36.9)	0.22	0.636
Statins	10 (52.6)	363 (64.8)	1.19	0.275
Other medications: NSAIDS	3 (15.8)	108 (19.3	0.14	0.706

Discussion

This retrospective study was conducted in King Abdullah Medical City (KAMC), Makkah, Saudi Arabia, to evaluate bleeding related to novel oral anticoagulants.

The present study found that the most commonly used NOACs were Edoxaban and Rivaroxaban, and the most common indication for their use was AF. The most frequently used medications were aspirin and stains with antiplatelets being used by 71.6% of patients. Among studied patients, after utilizing NOAC, only 1% experienced cerebral bleeding and 3.3% experienced GIT bleeding after taking NOAC. Only one patient experienced both UGIB and LGIB and only 1.2% experienced more bleeding after taking NOAC.

A retrospective cohort study was conducted in 2018 in five tertiary care hospital across three cities in Canada (Ottawa, Hamilton, Kingston) (18). This study revealed that the most common type of bleeding after using OAC (Dabigatran, Rivaroxaban, Apixaban, Warfarin) by TIMI defined major bleeds as intracranial hemorrhage and by ISTH as gastrointestinal bleeding and among patients with CRNMB hematuria the most common type and Dabigatran was the most common OAC cause of bleeding according to TIMI, ISTH, BARC (18).

Another study was done on patients who were prescribed dabigatran, rivaroxaban, or apixaban in a community teaching hospital in the United States (19). The study found that the majority of patients received NOAC for stroke prevention in AF and there were three bleeding incidents, one for each NOAC (19). In our study only 6 patients developed ICH.

A prospective observational study was carried out at 35 stroke units across Europe, the United States, and Asia (20). This study found that among patients who received Dabigatran, the rates of early recurrence of stroke event and major bleeding were 1.8% and 2.5% in those who received Rivaroxaban and their rates of occurrence was 2.9% in those who receive Apixaban (20). In Saudi Arabia, a retrospective cohort study was done in King Abdullah Medical City, a tertiary care center in the Makkah region. The study was carried out on patients who received Rivaroxaban from 2014 to 2019. The study found that the incidence of spontaneous ICH after using Rivaroxaban was 0.58% (21).

Limitations

The limitation of our study was being a single center study. This can hinder the generalization of the study results.

Conclusion

The present study found that the most commonly used NOACs was Edoxaban and Rivaroxaban, and the most common reason for usage was AF. Antiplatelets were used for about 71% of patients, with aspirin and stains the most common. Of studied patients, 1% had cerebral hemorrhage after NOAC use, 3.3% had GIT bleeding of whom 1.2% had UGIB and 2.4% had LGIB. Patients who had GIT hemorrhage after NOAC use had a significant higher percentage of those having a previous history of UGIB or LCIB than those who received Edoxaban as NOAC. Future multi-center studies done on larger sample size should be done to prove the safety, efficacy, and effectiveness of these drugs and to avoid drug-related problems in clinical practice.

Acknowledgment: The authors gratefully acknowledge the cooperation of Dr. Essam Hamdi Alahdal, Dr. Hatem Anis Abdullah, Dr. Abdulrahman Mohammed Aladani, Dr. Shahad Othman Bashihab, Dr. Sabir Ismail Jan Mohammad, Dr. Aseel Khalid Alhindi, Dr. Emad Aati Almuqati, Dr. Abdulrahman Anwar Noorelahi for their appreciated cooperation in data collection.

Funding: None

Conflicts of interest: no conflicts related to this work

References

1. Bauersachs R, Berkowitz SD, Brenner B, Buller HR, Decousus H, Gallus AS, et al. Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med 2010; 363: 2499-2510
2. Hylek EM, Evans-Molina C, Shea C, Henault LE, Regan S. Major hemorrhage and tolerability of warfarin in the fi rst year of therapy among elderly patients with atrial fi brillation. Circulation 2007; 115: 2689–2696.
3 Alberts MJ, Eikelboom JW, Hankey GJ. Antithrombotic therapy for stroke prevention in non-valvular atrial fibrillation. Lancet Neurol 2012; 11:1066-1081.
4. Rubboli A. Incidence, clinical impact and risk of bleeding during oral anticoagulation therapy. World J Cardiol. 2011; 3(11):351-358.
5. Peeters MT, Vroman F, Schreuder TA, van Oostenbrugge RJ, Staals J. Decrease in incidence of oral anticoagulant-related intracerebral hemorrhage over the past decade in the Netherlands. Eur Stroke J 2022;7(1):20-27.
6. Veltkamp R, Rizos T, Horstmann S. Intracerebral bleeding in patients on antithrombotic agents. Semin Thromb Hemost. 2013;39(8):963-971.
7.de Oliveira Manoel AL, Goffi A, Zampieri FG, Turkel-Parrella D, Duggal A, Marotta TR, et al. The critical care management of spontaneous intracranial hemorrhage: a contemporary review. Crit Care 2016;20:272-301.
8. Amin A. Oral anticoagulation to reduce risk of stroke in patients with atrial fibrillation: current and future therapies. Clin Interv Aging 2013;8:75-84.
9. Cheung KS, Leung WK. Gastrointestinal bleeding in patients on novel oral anticoagulants: Risk, prevention and management. World J Gastroenterol 2017 21;23(11):1954-1963.
10. Rubboli A, Becattini C, Verheugt FW. Incidence, clinical impact and risk of bleeding during oral anticoagulation therapy. World J Cardiol. 2011;3(11):351-358.
11. Kustos SA, Fasinu PS. Direct-Acting Oral Anticoagulants and Their Reversal Agents-An Update. Medicines (Basel). 2019 Oct 15;6(4):103-129.
12. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet 2014 15;383(9921):955-962.
13. Seiffge DJ, Werring DJ, Paciaroni M, Dawson J, Warach S, Milling TJ, et al. Timing of anticoagulation after recent ischaemic stroke in patients with atrial fibrillation. Lancet Neurol 2019;18(1):117-126.
14. Rahmat NA, Lip GY. Monitoring the Effects and Antidotes of the Non-vitamin K Oral Anticoagulants. Arrhythm Electrophysiol Rev 2015;4(2):90-95.
15. Yao X, Abraham NS, Sangaralingham LR, Bellolio MF, McBane RD, Shah ND, et al. Effectiveness and Safety of Dabigatran, Rivaroxaban, and Apixaban Versus Warfarin in Nonvalvular Atrial Fibrillation. J Am Heart Assoc 2016 13;5(6):e003725.
16. Gu ZC, Wei AH, Zhang C, Wang XH, Zhang L, Shen L, et al. Risk of Major Gastrointestinal Bleeding With New vs Conventional Oral Anticoagulants: A Systematic Review and Meta-analysis. Clin Gastroenterol Hepatol 2020;18(4):792-799.
17. McGrath ER, Go AS, Chang Y, Borowsky LH, Fang MC, Reynolds K, et al. Use of Oral Anticoagulant Therapy in Older Adults with Atrial Fibrillation After Acute Ischemic Stroke. J Am Geriatr Soc 2017;65(2):241-248.
18. Xu Y, Gomes T, Wells PS, Pequeno P, Johnson A, Sholzberg M. Evaluation of definitions for oral anticoagulant-associated major bleeding: A population-based cohort study. Thromb Res 2022;213:57-64
19. Alghadeer S, Hornsby L. Assessment of novel oral anticoagulant use within a community teaching hospital. Saudi Pharm J 2017;25(1):93-98.
20. Paciaroni M, Agnelli G, Falocci N, Tsivgoulis G, Vadikolias K, Liantinioti C, et al. Early Recurrence and Major Bleeding in Patients With Acute Ischemic Stroke and Atrial Fibrillation Treated With Non-Vitamin-K Oral Anticoagulants (RAF-NOACs) Study. J Am Heart Assoc 2017;6(12):e007034.
21. Alkhotani A, Alrishi N, Alharthi M, Alzahrani W. Rivaroxaban-associated intracranial hemorrhage in Saudi atrial fibrillation patients. Medicine (Baltimore) 2020 25;99(48):e23316.