ORIGINAL ARTICLE

COMPARISON OF DUAL VS. TRIPLE ANTITHROMBOTIC THERAPY IN NON-VALVULAR AF AND ACUTE CORONARY SYNDROME: A MALAYSIAN COHORT STUDY

Eldowaik Mohamed Salah Saad[1], Zainol Akbar Zainal[1], Shairyzah Ahmed Hisham[1], Sahimi Mohamed[2], Pavithira Devi[2]

[1]University of Cyberjaya, Selangor, Malaysia, [2]Hospital Sultan Idris Shah, Serdang, Malaysia

Objectives: This study aimed to compare Dual Antithrombotic Therapy (DAT) and Triple Antithrombotic Therapy (TAT) concerning bleeding and thrombosis outcomes in Malaysian patients with non-valvular atrial fibrillation (NVAF) and acute coronary syndrome (ACS), considering demographic characteristics and comorbidities.

Methodology: A retrospective observational cohort study was conducted at Hospital Serdang from January 1, 2020, to May 1, 2022. A total of 206 patients were selected via purposive sampling and divided into two groups. The TAT group received warfarin, clopidogrel, and aspirin, while the DAT group received warfarin and clopidogrel over a 1-year follow-up. Multivariate logistic regression analysis was employed.

Results: A higher incidence of thromboembolic episodes was observed in the DAT group (24.3% vs. 8.7% in the TAT group; adjusted odds ratio (aOR) 4.53, 95% CI 1.806-11.379, P= 0.001), signifying a 4.5-fold increase in thromboembolic events in DAT compared to TAT. Conversely, more bleeding episodes were observed in the TAT group (25.2% vs. 15.5% in the DAT group; aOR 2.22, 95% CI 0.993-4.970, P= 0.52), although the difference was not statistically significant.

Conclusion: The DAT protocol showed significantly more thrombosis episodes than the TAT protocol, while TAT exhibited a non-significant increase in bleeding events compared to DAT at one year follow-up in patients with NVAF and ACS.

Keywords: Acute coronary syndrome (ACS); Non-valvular atrial fibrillation (NVAF); Triple antithrombotic therapy (TAT); Dual antithrombotic therapy (DAT)

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INTRODUCTION

Acute coronary syndrome (ACS) is a subset of coronary artery disease (CAD) often triggered by plaque rupture within the coronary arteries, stemming from atherosclerosis. Common risk factors include smoking, hypertension, diabetes, hyperlipidemia, sedentary lifestyle, genetic predisposition, poor diet, and certain medications like sumatriptan and cocaine, which may precipitate coronary vasospasm.[1] The co-occurrence of ACS with acute stroke is prevalent.[2] Non-valvular atrial fibrillation (NVAF), not associated with mitral valve stenosis, surpasses valvular AF in occurrence.[3] AF, especially when concurrent with ACS, indicates higher long-term mortality.[4] Ischemic heart disease (IHD) can lead to AF, contributing to chronic coronary syndrome (CCS) or ACS.[5] Approximately 40% of individuals with AF also have CAD, and AF increases the risk of myocardial infarction in both CAD and non-CAD patients.[6] A notable proportion of ACS patients, particularly those undergoing PCI, also present with AF.[7]

Patients with combined AF and ACS share common risk factors for developing CAD, making their coexistence frequent.[8] AF complicates around 10% of acute myocardial infarction cases in the post-reperfusion era.[9] Despite advancements in treatment, a substantial proportion of AF patients also have CAD.[10] Anticoagulation initiation based on CHA_2DS_2VASc score is recommended, particularly in valvular AF (Table 1).[11] The HAS-BLED score helps assess

bleeding risk, aiding in clinical decision-making regarding anticoagulation.

Table 1: Initiation of anticoagulation based on CHA_2DS_2VASc score

Criteria	Male	Female	Initiation of anticoagulation
CHA_2DS_2VASc score	2	3	Recommended
	1	2	Considered
	0	1	Not recommended

Warfarin, owing to its cost-effectiveness and long-standing use, remains a preferred choice for many patients, especially the elderly.[12] However, transitioning from warfarin to non-vitamin K antagonist oral anticoagulants (NOACs) in the elderly population has been associated with an elevated risk of bleeding events[13]. Patients with NVAF at moderate-to-high risk of stroke require long-term oral anticoagulation, while those with ACS or undergoing PCI necessitate dual antiplatelet therapy (DAPT).[14] Balancing the benefits of combination antithrombotic therapy in preventing stroke and cardiac events against the increased bleeding risk poses a challenge.

DAT has been associated with a lower risk of bleeding compared to triple therapy. However, the decision between DAT and triple antithrombotic therapy (TAT) must carefully consider the balance between thrombosis prevention and bleeding risk. This study aims to compare the effectiveness and safety of TAT (warfarin, clopidogrel, and aspirin) versus DAT (warfarin and clopidogrel) in Malaysian patients with NVAF and ACS, focusing on bleeding and thrombosis outcomes.

METHODOLOGY

Study Design: This retrospective, single-centred, observational cohort study examines the association between antithrombotic therapy and thromboembolic events in adults with non-valvular atrial fibrillation (NVAF) and ACS.

Setting: The study was conducted at Hospital Serdang in Malaysia, providing a comprehensive view of patient outcomes within a specific healthcare context.

Participants: The study included adults aged 18 years and older with NVAF and ACS who were admitted to Hospital Serdang between January 1, 2020, and May 1, 2022.

Variables: The primary predictor variable was the type of antithrombotic therapy received (TAT or DAT). The primary outcome variable was the occurrence of thromboembolic events (ischemic stroke or recurrent ACS). Secondary outcomes included bleeding events such as gastrointestinal or intracranial bleeding.

Data Sources/Measurement: Data were collected retrospectively from the hospital's electronic medical records system (E-HIS). The data collection form comprised six parts, covering general and demographic data, clinical aspects, laboratory investigations, medication usage, tools/models/scores for outcome prediction, and clinical outcomes.

Bias: To minimize bias, a 1:1 propensity score-matched cohort was employed to match patients based on potential confounders. Additionally, purposive sampling was used for patient selection.

Study Size: Sample size estimation was based on the principle of 10 events per variable (EPV), resulting in a target sample size of 206 patients. This size ensured adequate statistical power to detect associations between antithrombotic therapy and outcomes.

Quantitative Variables:

Quantitative variables included demographic characteristics, comorbidities, laboratory parameters, medication usage, and outcome measures such as thromboembolic and bleeding events.

Statistical Methods: Descriptive and inferential statistical analyses were performed using SPSS software version 25. Statistical tests included Pearson's Chi-square test, Fisher's Exact test, independent t-test, Mann-Whitney U test, and logistic regression. A significance level of $p < 0.05$ and a 95% confidence interval were used to interpret the results, ensuring robustness and reliability in the analysis.

RESULTS

Participants: The study included a total of 206 adults with NVAF and ACS admitted to Hospital Serdang in Malaysia. The mean and median age of the patients was approximately 62 years, with a standard deviation of 11.5 years. The majority of patients were male (55.8%), and Malay ethnicity was most prevalent (38.3%), Table 2.

Descriptive Data: Among the patients, 73.3% had hypertension, 47.5% presented with unstable angina, and the distribution of heart failure with different ejection fractions was observed, with 47% having preserved ejection fractions, 34.47% reduced ejection fractions, and 18.45% mildly reduced ejection fractions. Additionally, 57.28% of the patients were non-diabetic, and 49.51% had chronic kidney disease (CKD). The median CHA_2DS_2-VASC score and HAS-BLED score were 4 and 2, respectively (Table 2).

Table 2: Patient demographic information and clinical information based on the type of antithrombotic regimen received

Study Variables	Antithrombotic regimen		P-Value
	DAT	TAT	
Total (N)	**103**	**103**	**-**
Median age (years)	63 [54-68]	61 [55-68]	0.904
Median CHA_2DS_2-VASC score	4 [3-5]	4 [4-5]	0.358
Median HAS-BLED score	1 [1-3]	2 [1-3]	0.109
Gender			
Man	57(49.6%)	58(50.4%)	0.88
Woman	46(50.5%)	45(49.5%)	
Ethnicity			
Malay	38(48.1%)	41(51.9%)	
Chinese	31(56.4%)	24(43.6%)	0.753
Indian	30(47.6%)	33(52.4%)	
Others	4(44.4%)	5(55.6%)	
Hypertension			
No	28(50.9%)	27(49.1%)	0.875
Yes	75(49.7%)	76(50.3%)	
Acute coronary syndrome			
NSTE-ACS	83(50.6%)	81(49.4%)	0.729
STEMI	20(47.6%)	22(52.4%)	
HFpEF			
EF ≥ 40%	66(48.9%)	69(51.1%)	0.66
EF< 40%	37(52.1%)	34(47.9%)	
Diabetes Mellitus	41(46.6%)	47(53.4%)	0.398
CKD (eGFR)	20(52.6%)	18(47.4%)	0.719
PCI	64(52.5%)	58(47.5%)	0.395

NSTE-ACS: "non-ST- segment elevation ACS"; STE-ACS: "ST-segment elevation ACS"; HFrEF: "heart failure reduced ejection fraction"; Advanced CKD: "advanced chronic kidney disease (eGFR <30)"; PCI: "percutaneous coronary intervention"

Outcome Data: The primary outcome of the study was the occurrence of thromboembolic events, which showed a statistically significant correlation with the type of antithrombotic regimen received and heart failure characterized by lower ejection fraction. Thromboembolic events were significantly more frequent in patients with heart failure and reduced ejection fraction compared to those with preserved or mildly reduced ejection fraction. However, there was no statistically significant association between bleeding events and the type of antithrombotic regimen (Table 3).

Main Results: Statistical analyses revealed a significant association between patients receiving DAT and the occurrence of thromboembolic events compared to those receiving TAT. Patients in the DAT group were 4.5 times more likely to experience thromboembolic events than those in the TAT group after adjusting for other factors. Additionally, age, hypertension, heart failure with reduced ejection fraction, and diabetes mellitus were identified as significant predictors of thromboembolic events. However, there was no statistically significant difference in the occurrence of bleeding events between the TAT and DAT groups, although a trend towards higher bleeding frequency was observed in the TAT group (Table 4).

Table 3: The multivariate logistic regression predicting the likelihood of reporting thromboembolic events and bleeding events

	OR [95% CI]	P-value
Thromboembolic events		
DAT	4.44 [1.781-11.084]	0.001
Age	1.072 [1.018-1.129]	0.008
Female	1.804 [0.749-4.345]	0.188
Hypertension	4.57 [1.45-14.4]	0.009
HFrEF	5.49 [2.193-13.77]	<0.001
Diabetes	4.93 [1.838-13.257]	0.002
Bleeding events		
DAT	2.187 [0.984-4.859]	0.055
Age	1.087 [1.036-1.141]	0.001
Female	0.809 [0.365-1.793]	0.601
Hypertension	3.05 [1.106-8.456]	0.031
HFrEF	0.932 [0.4-2.175]	0.871
Diabetes	2.717 [1.147-6.437]	0.023

HFrEF: "heart failure reduced ejection fraction"; DAT: "dual antiplatelet therapy"; OR: "odds ratio"; CI: "confidence interval"

DISCUSSION

In this study, a significant disparity in thromboembolic events was observed between patients receiving DAT and TAT. The TAT group exhibited a notably lower incidence of thromboembolic events, indicating a 36% reduction in thromboembolic risk compared to the DAT group. This finding aligns with previous research, supported by a meta-analysis demonstrating an increase in recurrent myocardial infarction episodes with DAT compared to TAT.[15] However, it contrasts with findings from other trials such as the WOEST trial, which showed a lower occurrence of bleeding events with DAT but no significant difference in thromboembolic events compared to TAT.[11,12]

Conversely, regarding bleeding events, our study found a higher incidence in the TAT group, although not statistically significant. Adjusted analysis revealed a 61% reduction in bleeding risk in the DAT group, highlighting a potential benefit of DAT over TAT. These findings differ from some previous studies, including meta-analyses, which reported fewer bleeding episodes with DAT compared to TAT. The discrepancy may suggest the need for further investigation, particularly with extended follow-up periods.[16]

Table 4: The relation between patients' demographics and clinic information and antithrombotic types based on the thromboembolic events as the primary outcome

Study Variables	Thromboembolic event		P-value	Bleeding event		P-value
	No	Yes		No	Yes	
Antithrombotic Regimen						
DAT	78(75.5%)	25(24.3%)	0.003	87(84.5%)	16(15.5%)	0.084
TAT	94(91.3%)	9(8.7%)		77(74.8%)	26(25.2%)	
Median Age (years)	61 [55-67]	66 [57-72]	0.032	60 [53-67]	67 [62-73]	<0.001
Sex						
Male	99(86.1%)	16(13.9%)	0.26	92 (80%)	23 (20%)	0.876
Female	73(80.2 %)	18(19.8%)		72 (79.1%)	19 (20.9%)	
Ethnicity						
Malay	67(84.8%)	12(15.2%)	0.949	63(79.7%)	16(20.3%)	0.343
Chinese	46(83.6%)	9(16.4%)		45(81.8%)	10(18.2%)	
Indian	52(82.5%)	11(17.5%)		47(74.6%)	16(25.4%)	
Others	7(77.8%)	2(22.2%)		9(100%)	0(0%)	
Hypertension						
No	49(89.1%)	6(10.9%)	0.192	46(83.6%)	9(16.4%)	0.387
Yes	123(81.5%)	28(18.5%)		118(78.1%)	33(21.9%)	
Acute coronary syndrome						
NSTE-ACS	139(84.8%)	25(15.2%)	0.335	124(75.6%)	40(24.4%)	0.005
STEMI	33(78.6%)	9(21.4%)		40(95.2%)	2(4.8%)	
HFpEF						
EF ≥ 40%	122(90.4%)	13(9.6%)	0.001	110(81.5%)	25(18.5%)	0.358
EF< 40%	50(70.4%)	21(29.6%)		54(76.1%)	17(23.9%)	
Diabetes Mellitus						
No	102(86.4%)	16(13.6%)	0.187	97(82.2%)	21(17.8%)	0.285
Yes	70(79.5%)	18(20.5%)		67(76.1%)	21(23.9%)	
CKD (eGFR)						
No	142(84.5%)	26(15.5%)	0.403	145(86.3%)	23(13.7%)	<0.001
Yes	30 (78.9%)	8(21.1%)		19(50%)	19(50%)	

NSTE-ACS: "non-ST- segment elevation ACS"; STE-ACS: "ST-segment elevation ACS"; HFrEF: "heart failure reduced ejection fraction"; Advanced CKD: "advanced chronic kidney disease (eGFR <30)"; PCI: "percutaneous coronary intervention"

The association between demographic variables and bleeding/thromboembolic events revealed several noteworthy trends. Advancing age correlated positively with both thromboembolic and bleeding events, consistent with existing literature. However, while the risk of thromboembolic events increased with age, the proportion of ischemic events relative to severe bleeding events decreased. Gender did not significantly affect thromboembolic or bleeding events, contrary to findings suggesting differing risk profiles in men and women.

Hypertension emerged as a significant predictor for both thromboembolic and bleeding events, with individuals with hypertension experiencing higher occurrences of both. This aligns with prior research demonstrating an increased risk of ischemic and hemorrhagic stroke in hypertensive patients with AF.[17,18] Effective blood pressure management is therefore crucial in reducing stroke and bleeding risk in AF patients.[19]

Type of heart failure also influenced thromboembolic events, with HFpEF patients exhibiting a significantly higher risk compared to those with preserved EF. However, no significant association was found between heart failure type and bleeding events. These findings support the importance of considering heart failure subtype in thromboembolic risk assessment.

Diabetes mellitus emerged as a significant risk factor for increased thromboembolic and bleeding events. Diabetic patients had approximately five times higher thromboembolic risk and nearly three times higher bleeding risk compared to non-diabetic patients.[20-23] These results underscore the need for tailored management strategies for diabetic AF patients to mitigate both thrombotic and bleeding risks.

Advanced CKD did not show a significant association with thromboembolic events but was significantly correlated with a higher risk of bleeding events. This aligns with previous research indicating a heightened susceptibility to bleeding events in patients with severe CKD, particularly during treatment for CAD or AF.[24-27]

LIMITATION

Several limitations were identified in this study. Firstly, the data was collected from a single-center, which may limit the generalizability of the findings to other populations. Additionally, the small sample size might have restricted the statistical power of the analysis and increased the risk of type II error. Being

a retrospective cohort study, there were inherent limitations related to data collection and potential biases. Despite applying the propensity score matching model to control for known confounders, residual confounding factors may still exist, affecting the validity of the results.

CONCLUSION

In conclusion, this study comparing DAT and TAT in Malaysian patients with NVAF and ACS highlights the importance of personalized antithrombotic management. While DAT demonstrated a higher incidence of thromboembolic events, TAT exhibited a trend towards increased bleeding episodes, albeit not statistically significant. These findings underscore the necessity of balancing thrombotic and bleeding risks based on individual patient characteristics. Subgroup analyses revealed associations between hypertension, heart failure, diabetes mellitus, advanced CKD, and heightened thromboembolic or bleeding events, emphasizing the need for tailored therapeutic approaches.

AUTHORS' CONTRIBUTION

EMSS and ZAZ: Concept and design, data acquisition, interpretation, drafting, final approval, and agree to be accountable for all aspects of the work. EMSS, ZAZ, SAH, SM, and PD: Data acquisition, interpretation, drafting, final approval and agree to be accountable for all aspects of the work.

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REFERENCES

1. Zafar F, Tariq W, Shoaib R, Shah A, Siddique M, Zaki A, et al. Frequency of ischemic stroke subtypes based on toast classification at a tertiary care center in Pakistan. Asian J Neurosurgery. 2018;13(4):984-9.
2. Rashid MH, Yaseen G, Ghaffar U, Khan AA, Kabir A, Aisha A, et al. Prevalence of Acute Coronary Syndrome and Various Risk Factors in Acute Stroke Patients. Cureus. 2020;12(8):e9552.
3. Ahmed I, Nasir A, Shams P, Shahab H, Hassan M, Subhani F, et al. Clinical characteristics and prognostic factors of atrial fibrillation at a tertiary center of Pakistan-From a South-Asian perspective-A cross-sectional study. Annals Med Surg. 2022;73:103128.
4. Windecker S, Lopes RD, Massaro T, Jones-Burton C, Granger CB, Aronson R, et al. Antithrombotic therapy in patients with atrial fibrillation and acute coronary syndrome treated medically or with percutaneous coronary intervention or undergoing elective percutaneous coronary intervention: insights from the AUGUSTUS trial. Circulation. 2019;140(23):1921-32.
5. Suo N, Yang YM, Wang J, Zhang H, Shao XH, Wu S, et al. Evolving antithrombotic treatment patterns for patients with nonvalvular atrial fibrillation and acute coronary syndrome or underwent percutaneous coronary intervention in China: a cross-sectional study. Frontiers Cardiovasc Med. 2022;9:846803.
6. Camm A J, Accetta G, Ambrosio G, Atar D, Bassand JP, Berge E, et al. Evolving antithrombotic treatment patterns for patients with newly diagnosed atrial fibrillation. Heart. 2017;103(4):307-14.
7. Potpara TS, Lip GY, Dagres N, Crijns HJ, Boriani G, Kirchhof P, et al. Cohort profile: the ESC EURObservational Research Programme Atrial Fibrillation III (AF III) Registry. European Heart Journal - Qual Care Clin Outcomes. 2021;7(3):229-37.
8. Wolfes J, Ellermann C, Frommeyer G, & Eckardt L. Evidence-based treatment of atrial fibrillation around the globe: comparison of the latest ESC, AHA/ACC/HRS, and CCS guidelines on the management of atrial fibrillation. Reviews Cardiovasc Med. 2022;23(2):56.
9. Smith Jr SC, Feldman TE, Hirshfeld Jr JW, Jacobs AK, Kern MJ, King III SB, et al. ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/SCAI writing committee to update the 2001 guidelines for percutaneous. J Am Coll Cardiol. 2006;47(1):e1-121.
10. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS) The Task Force for the diagnosis and management of atrial fibrillation of the European. Eur Heart J. 2021;42(5):373-498.
11. Moustafa A, Khan M, Saud M, Abdalla AM, Amer B, Muhammad S. Safety and efficacy of dual versus triple antithrombotic therapy in Patients with atrial fibrillation undergoing percutaneous coronary intervention: a meta-analysis. Avicenna J Med. 2020;10(4):232-40.
12. van Rein N, Heide-Jørgensen U, Lijfering WM, Dekkers OM, Sørensen HT, Cannegieter SC. Major bleeding rates in atrial fibrillation patients on single, dual, or triple antithrombotic therapy: results from a Nationwide Danish Cohort Study. Circulation. 2019;139(6):775-86.
13. Leon MB, Baim DS, Popma JJ, Gordon PC, Cutlip DE, Ho KK, et al. A clinical trial comparing three antithrombotic-drug regimens after coronary-artery stenting. New Eng J Med. 1998;339(23):1665-71.
14. Connolly S, Pogue J, Hart R, Pfeffer M, Hohnloser S, Chrolavicius S, et al. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial. Lancet. 2006;367(9526):1903-12.
15. Luo CF, Mo P, Li GQ, Liu SM. Aspirin-omitted dual antithrombotic therapy in non-valvular atrial fibrillation patients presenting with acute coronary syndrome or undergoing percutaneous coronary intervention: results of a meta-analysis. European Heart Journal - Cardiovasc Pharmacother. 2021;7(3): 218-24.
16. Dharma S. Double Antithrombotic versus Triple Antithrombotic Therapy in Patients with Atrial Fibrillation and Acute Coronary Syndrome. Inter J Angiol. 2020;29(02):081-087.
17. Dewilde WJ, Oirbans T, Verheugt FW, Kelder JC, De Smet BJ, Herrman JP, et al. Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing

percutaneous coronary intervention: an open-label, randomised, controlled trial. Lancet. 2013;381(9872):1107-15.
18. Golwala H, Jackson II L R, Simon DN, Piccini JP, Gersh B, Go AS, et al. Racial/ethnic differences in atrial fibrillation symptoms, treatment patterns, and outcomes: Insights from Outcomes Registry for Better Informed Treatment for Atrial Fibrillation Registry. Am Heart J. 2016; 174:29-36.
19. Li L, Geraghty OC, Mehta Z, Rothwell PM. Age-specific risks, severity, time course, and outcome of bleeding on long-term antiplatelet treatment after vascular events: a population-based cohort study. Lancet. 2017;390(10093):490-9.
20. Haider A, Bengs S, Luu J, Osto E, Siller-Matula JM, Muka T, et al. Sex and gender in cardiovascular medicine: presentation and outcomes of acute coronary syndrome. Eur Heart J. 2020;41(13):1328-36.
21. Harskamp RE, Lucassen WA, Lopes RD, Himmelreich JC, Parati G, Weert HCV. Risk of stroke and bleeding in relation to hypertension in anticoagulated patients with atrial fibrillation: a meta-analysis of randomised controlled trials. Acta Cardiologica. 2022;77(3):191-5.
22. Mentias A, Briasoulis A, Shantha G, Alvarez P, Vaughan-Sarrazin M. Impact of heart failure type on thromboembolic and bleeding risk in patients with atrial fibrillation on oral anticoagulation. Am J Cardiol. 2019;123(10):1649-53.
23. Sethi SS, Akl EG, Farkouh ME. Diabetes mellitus and acute coronary syndrome: lessons from randomized clinical trials. Current Diabetes Reports. 2012;13:294-304.
24. Peng YL, Leu HB, Luo JC, Huang CC, Hou MC, Lin HC, et al. Diabetes is an independent risk factor for peptic ulcer bleeding: A nationwide population?based cohort study. J Gastroenterol Hepatol. 2013;28(8):1295-9.
25. Moisi MI, Rus M, Bungau S, Zaha DC, Uivarosan D, Fratila O, et al. Acute coronary syndromes in chronic kidney disease: clinical and therapeutic characteristics. Medicina. 2020;56(3):118.
26. Burlacu A, Genovesi S, Goldsmith D, Rossignol P, Ortiz A, Kalra PA, et al. Bleeding in advanced CKD patients on antithrombotic medication-a critical appraisal. Pharmacol Res. 2018;129:535-43.
27. Mahady SE, Polekhina G, Woods RL, Wolfe R, Wetmore JB, Margolis KL, et al. Association Between CKD and Major Hemorrhage in Older Persons: Data From the Aspirin in Reducing Events in the Elderly Randomized Trial. Kidney Inter Rep. 2023;8(4):737-45.

Address for Correspondence:

Mr. Eldowaik Mohamed Salah Saad, Department of Hospital and Clinical Pharmacy, Faculty of Pharmacy, University of Cyberjaya, Selangor, Malaysia.
Email: mohamed7720092013aldowaik@gmail.com