

Factors influencing upper gastrointestinal bleeding in geriatric coronary heart disease patients taking low-dose aspirin

Shinta Khoirun Nisa^{1*}, Mustofa², I Dewa Putu Pramantara Setiabudi³

¹Master of Clinical Pharmacy, Faculty of Pharmacy, Universitas Gadjah Mada, Yogyakarta,

²Department of Pharmacology and Therapy, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, ³Division of Geriatrics, Department of Internal Medicine, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada/Dr. Sardjito General Hospital, Yogyakarta

<https://doi.org/10.22146/ijpther.18642>

ABSTRACT

Submitted: 22-12-2024

Accepted : 06-01-2025

Keywords:

gastrointestinal bleeding;
geriatric;
low-dose aspirin;
antiplatelet;
coronary heart disease

Geriatric patients are a special group that requires special attention in monitoring drug side effects. Low-dose aspirin use over an extended period of time increases the risk of upper gastrointestinal bleeding (UGIB). Identification of factors that influence UGIB is important to improve accuracy in selecting and monitoring drug therapy in geriatric patients. This study aimed to identify the variables that affect the incidence of UGIB in geriatric patients with coronary heart disease (CHD) who use antiplatelet. This study used a case-control design. Secondary data were obtained retrospectively from the medical records of CHD patients in the Dr. Sardjito General Hospital, Yogyakarta from January 2022 to June 2024. As cases were a group of inpatient CHD who received low-dose aspirin therapy and experienced UGIB, while as controls were outpatient CHD with the similar characteristics without UGIB. The data was analyzed using the Chi-Square and multiple logistic regression analysis. Bivariate analysis showed that hypertension ($p = 0.003$; OR 5.469; 95% CI 1.883-15.884) and the use of dual antiplatelet therapy/DAPT ($p = 0.003$; OR 10.075; 95% CI 2.052-49.469) were the risk factors that significantly affected the incidence of UGIB. However, further multivariate analysis demonstrated no single factor had the biggest impact on UGIB. In conclusion, risk factor that influence UGIB in the use of antiplatelet aspirin by geriatric patients with CHD are comorbid of hypertension and the use of DAPT.

ABSTRAK

Pasien geriatri merupakan populasi khusus yang memerlukan perhatian khusus dalam pemantauan efek samping obat. Penggunaan aspirin dosis rendah jangka panjang mempunyai risiko perdarahan saluran cerna bagian atas (PSCBA). Identifikasi faktor-faktor yang mempengaruhi PSCBA penting dilakukan untuk meningkatkan ketepatan dalam pemilihan dan pemantauan terapi obat pada pasien geriatri. Penelitian ini bertujuan untuk mengidentifikasi variabel yang mempengaruhi PSCBA pada pasien geriatri dengan penyakit jantung koroner (PJK) yang diterapi antiplatelet. Penelitian ini menggunakan rancangan kasus-kontrol. Data sekunder diperoleh secara retrospektif dari rekam medis pasien PJK di RSUP Dr. Sardjito, Yogyakarta pada bulan Januari 2022 sampai dengan Juni 2024. Sebagai kasus merupakan kelompok pasien PJK rawat inap yang mendapatkan terapi aspirin dosis rendah dan mengalami PSCBA, sedangkan sebagai kontrol merupakan pasien PJK rawat jalan dengan karakteristik yang sama tanpa PSCBA. Data dianalisis menggunakan uji chi square dan analisis regresi logistik ganda. Analisis bivariat menunjukkan bahwa hipertensi ($p = 0,003$; OR 5,469; 95%CI: 1,883-15,884) dan penggunaan terapi antiplatelet ganda/DAPT ($p = 0,003$; OR 10,075; 95% CI: 2,052-49,469) merupakan penyebab PSCBA. Namun, analisis multivariat lebih lanjut menunjukkan tidak ada faktor tunggal yang memiliki dampak terbesar pada PSCBA. Sebagai kesimpulan, faktor risiko yang memengaruhi PSCBA pada penggunaan antiplatelet aspirin oleh pasien geriatri dengan PJK adalah komorbiditas hipertensi dan penggunaan DAPT.

*corresponding author: shinta.khoirun.n@mail.ugm.ac.id

INTRODUCTION

Geriatric patients are one of the populations that require special attention in selecting drug therapy and monitoring its side effects. One of the most common drugs that cause adverse drug reaction in geriatric patients is antiplatelets.¹ Low-dose aspirin is the first-line antiplatelet and is used by almost all coronary heart disease (CHD) patients.^{2,3} However, using low-dose aspirin for an extended period of time increases the risk of gastrointestinal bleeding (GIB), particularly in the upper gastrointestinal tract.

In some cases, geriatric patients have more than one disease. Upper gastrointestinal bleeding (UGIB) adverse effects are more likely to occur in this condition. When taking low-dose of aspirin, comorbid of hypertension and diabetes mellitus (DM) are separate risk factors for GIB.⁴ Furthermore, patients who regularly take low-dose aspirin are at significant risk for GIB when combined with thienopyridine medications (such as clopidogrel) with a hazard ratio (HR) of 2.30.⁵ The increased risk of bleeding is also associated with smoking status. Patients with a history of smoking and those who smoke currently are more likely to experience GIB (active smokers have an HR of 2.12).⁶ Based on this information, geriatric patients with CHD are more likely to experience UGIB. However, not all patients who receive antiplatelet therapy will experience bleeding. Identification of factors that influence UGIB is important to improve accuracy in selecting and monitoring drug therapy in geriatric patients.

MATERIAL AND METHODS

Design and subjects

This research is an analytical observational study and uses a case-control approach. The research data

are in the form of secondary data taken retrospectively from the medical records of CHD patients from January 2022 to June 2024. A group of inpatient CHD patients who received low-dose aspirin therapy and were diagnosed by a doctor as having UGIB were selected as a case, while those selected as controls were a group of outpatient CHD patients with the same characteristics as the case group but were not diagnosed by a doctor as having UGIB. The control group was selected by matching (1:1) based on age and gender.

Procedure

Patients with sepsis, those on gastroprotective medications like PPI or H2RA, and those with insufficient medical record data are all excluded from this study. A fill-out data collection sheet regarding CHD patients receiving antiplatelet aspirin was the tool used in this study. The data to be taken include: medical record number, date of birth, gender, primary diagnosis, antiplatelet drug data (drug name, dose, duration of administration), comorbid diseases, clinical manifestation of UGIB (hematemesis or melena).

Data analysis

Based on the calculation results for each risk factor, it was obtained that the minimum number of sample was 30 subjects. Thus, this study uses n of 30 for each group. The chi square test was used in this study's data analysis, followed by a multiple logistic regression test.

RESULTS

Patients who registered between 2022 and 2024 were the subjects of the data collection. The data analysis included 66 patients in total who fulfilled the study's inclusion and exclusion criteria. Of the 66 patients, 33 patients

experienced UGIB (case group) and 33 patients did not experience bleeding (control group). TABLE 1 shows the subjects' baseline characteristics.

Patients' baseline characteristics were categorized by age, gender, comorbidity between DM and hypertension, smoking status, and DAPT use. According to TABLE 1, patients in the case group were on average 68 yo, whereas those in the control group were 69 yo. With a frequency of 78.78%, male patients are more likely than female patients to experience UGIB. Additionally, TABLE 1 shows that among individuals taking low-dose aspirin, hypertension and DM are comorbidities linked to UGIB. The percentage of patients with hypertension comorbidity reached 63.63% and 30.30% with DM in the case group. The study's findings showed that 57.57% of the patients in the case group were smokers. Patients who receive DAPT are at higher risk of experiencing UGIB than those receiving single antiplatelet therapy (SAPT) with a

percentage of 93.93%.

Bivariate analysis

The results of the bivariate analysis in TABLE 2 shows that the risk factors that significantly influence the incidence of UGIB are comorbid of hypertension and the use of DAPT ($p < 0.05$). Patients with comorbid of hypertension had a 5.4 times higher risk of experiencing UGIB than patients without comorbid of hypertension ($p = 0.003$; OR = 5.469; 95% CI: 1.883-15.884). The hypertension variable has a wide 95% CI value of 1.8 to 15.8 so that the bivariate results for comorbid of hypertension cannot represent the actual population conditions. TABLE 2 also shows that patients using DAPT have a 10 times higher risk of experiencing UGIB than patients using SAPT ($p = 0.003$; OR = 10.075; 95% CI: 2.052-49.469). The DAPT variable has a wide 95% CI value of 2 to 49.4 so that the bivariate results for the use of DAPT cannot represent the actual population conditions.

TABLE 1. Baseline subject characteristics

Variables	Case (n=33)	Control (n=33)
Age (mean \pm SD yr)	68.8 \pm 5.9	69.1 \pm 5.5
Gender [n (%)]		
• Male	26 (78.78)	26 (78.78)
• Female	7 (21.21)	7 (21.22)
Hypertension [n (%)]		
• Yes	21 (63.63)	8 (24.25)
• No	12 (36.36)	25 (75.75)
Diabetes mellitus [n (%)]		
• Yes	10 (30.30)	7 (21.22)
• No	23 (69.69)	26 (78.78)
Smoking status [n (%)]		
• Yes	19 (57.57)	15 (45.46)
• No	14 (42.42)	18 (54.54)
Use of DAPT [n (%)]		
• Yes	31 (93.93)	20 (60.61)
• No	2 (6.06)	13 (39.39)

TABLE 2. Bivariate analysis result

Variable	Case	Control	p	OR	95%CI
Hypertension [n (%)]					
• Yes	21 (63.63)	8 (24.25)	0.003	5.469	1.883-15.884
• No	12 (36.37)	25 (75.75)			
Diabetes mellitus [n (%)]					
• Yes	10 (30.30)	7 (21.22)	0.573	1.615	0.528-4.935
• No	23 (69.70)	26 (78.78)			
Smoking status [n (%)]					
• Yes	19 (57.57)	15 (45.46)	0.460	1.629	0.616-4.308
• No	14 (42.43)	18 (54.54)			
Use DAPT					
• Yes	31 (93.93)	20 (60.60)	0.003	10.075	2.052-49.469
• No	2 (6.07)	13 (39.40)			

TABLE 3. Results of multivariate analysis

Variables	p	Exp (B)	95% CI
Hypertension	0.054	3.150	0.978-10.143
Use of DAPT	0.053	5.417	0.981-29.917

The bivariate results further show that there is no statistically significant correlation between the incidence of GIB and the DM variable. However, an OR score > 1 indicates that the variable clinically has a strong association to the incidence of GIB (p = 0.573; OR = 1.615; 95% CI: 0.528-4.935). There was no significant correlation between the smoking variable and the incidence of GIB (p = 0.460). The smoking variable had an OR value of 1.629, meaning that patients who smoke have a 1.629 times higher risk of experiencing UGIB than patients who do not smoke.

Multivariate analysis

The multivariate analysis demonstrated that there is no factor that has the greatest influence on the dependent variable (p>0.05).

DISCUSSION

In this study, male patients are at higher risk of experiencing UGIB than females. This is consistent with research by Luo *et al.*,⁵ that found that male gender is one of the independent risk factors for the development of UGIB in aspirin users. Other research has also revealed similar findings. An independent risk factor for increased bleeding in low-dose aspirin users is male gender.⁷

Comorbid of hypertension and DAPT use are the factors that affect UGIB, according to the findings of bivariate analysis. The findings of this study are consistent with Mahady *et al.*,⁶ analysis. One of the risk factors that increases gastrointestinal bleeding in geriatric patients using aspirin is hypertension.⁶ Another study with subjects who were not aspirin users reported that an important

predictive factor for gastrointestinal bleeding was hypertension.⁸ The possible underlying mechanism is the production of nitric oxide (NO) due to mechanotransduction induction. One substance that is crucial in avoiding improper thrombus development is nitric oxide.⁹

In a study, it was reported that patients given DAPT were more susceptible to progressive gastrointestinal injury than patients receiving the antiplatelet aspirin alone.¹⁰ With percentages of 10.8% and 3.6%, respectively, the incidence of serious bleeding or life-threatening bleeding was also higher in patients using DAPT than SAPT.¹¹

Comorbid of diabetes mellitus was linked to a higher risk of gastrointestinal bleeding among low-dose aspirin users, according to one meta-analysis research, with an OR value of 3.10 (95% CI, 2.35-4.09).⁴ In diabetic hyperglycemia patients, there is a relative decrease in oxidized Hb due to an increase in glycosylated Hb. This causes reduced oxygen absorption by the tissue and further chronic hypoxia of the gastric mucosa. This condition will lead to gastric bleeding. Furthermore, during hypoxic stress, there is an increase in the release of stress hormones like catecholamines. These hormones also play a role in damage to the gastric mucosal barrier.¹²

Smoking is one of the risk factors linked to a higher frequency of gastrointestinal bleeding, according to a study conducted on aspirin users who were at least 70 years old.⁶ Another study on subjects who were not aspirin users also showed similar results. Among active smokers, the risk of gastrointestinal bleeding increased with an HR value of 2.20. (95% CI 1.84-2.62).¹³ Smoking can affect the balance of HCl and sodium bicarbonate in the digestive system. HCl secretion increases accompanied by decreased bicarbonate production.¹⁴

CONCLUSION

Factors that influence UGIB in geriatric patients with CHD taking low dose aspirin are comorbid of hypertension and the use of DAPT.

ACKNOWLEDGMENT

Author would like to thank the Director of Dr. Sardjito Hospital for the permission to perform this study.

REFERENCES

1. Nair NP, Chalmers L, Peterson GM, Bereznicki BJ, Castellino RL, Bereznicki LR. Hospitalization in older patients due to adverse drug reactions -the need for a prediction tool. *Clin Interv Aging* 2016; 11:497-505. <https://doi.org/10.2147/CIA.S99097>
2. Lavie CJ, Howden CW, Scheiman J, Tursi J. Upper Gastrointestinal Toxicity Associated With Long-Term Aspirin Therapy: Consequences and Prevention. *Curr Probl Cardiol* 2017; 42(5):146-64. <https://doi.org/10.1016/j.cpcardiol.2017.01.006>
3. Hira RS, Gosch KL, Kazi DS, Yeh RW, Kataruka A, Maddox TM, et al. Potential Impact of the 2019 ACC/AHA Guidelines on the Primary Prevention of Cardiovascular Disease Recommendations on the Inappropriate Routine Use of Aspirin and Aspirin Use Without a Recommended Indication for Primary Prevention of Cardiovascular Disease in Cardiology Practices: Insights From the NCDR PINNACLE Registry. *Circ Cardiovasc Qual Outcomes* 2022; 15(3):e007979. <https://doi.org/10.1161/CIRCOUTCOMES.121.007979>
4. Wang Y, Wang W, Wang B, Wang Y. The Risk of Gastrointestinal Hemorrhage in Low-Dose Aspirin Users with

- Diabetes Mellitus: Systematic Review and Meta-Analysis. *Gastroenterol Res Pract* 2020; 2020:9824615.
<https://doi.org/10.1155/2020/9824615>
5. Luo PJ, Lin XH, Lin CC, Luo JC, Hu HY, Ting PH, *et al.* Risk factors for upper gastrointestinal bleeding among aspirin users: An old issue with new findings from a population-based cohort study. *J Formos Med Assoc* 2019; 118(5):939-44.
<https://doi.org/10.1016/j.jfma.2018.10.007>
6. Mahady SE, Margolis KL, Chan A, Polekhina G, Woods RL, Wolfe R, *et al.* Major GI bleeding in older persons using aspirin: incidence and risk factors in the ASPREE randomised controlled trial. *Gut* 2021; 70(4):717-24.
<https://doi.org/10.1136/gutjnl-2020-321585>
7. Whitlock EP, Burda BU, Williams SB, Guirguis-Blake JM, Evans CV. Bleeding Risks With Aspirin Use for Primary Prevention in Adults: A Systematic Review for the U.S. Preventive Services Task Force. *Ann Intern Med* 2016; 164(12):826-35.
<https://doi.org/10.7326/M15-2112>
8. Kiattiweerasak A, Bongkotvirawan P, Aumpan N, Yamaoka Y, Miftahussurur M, Vilaichone RK. Predictive factors and prognosis of upper gastrointestinal bleeding in gastric cancer: A large population-based study (UGIB-GC trial). *PLoS One* 2023; 18(9):e0291926.
<https://doi.org/10.1371/journal.pone.0291926>
9. Chirkov YY, Nguyen TH, Horowitz JD. Impairment of Anti-Aggregatory Responses to Nitric Oxide and Prostacyclin: Mechanisms and Clinical Implications in Cardiovascular Disease. *Int J Mol Sci* 2022; 23(3):1042.
<https://doi.org/10.3390/ijms23031042>
10. He C, Li Y, Jiang X, Jiang MN, Zhao XX, Ma SR, *et al.* Progression of Gastrointestinal Injury During Antiplatelet Therapy After Percutaneous Coronary Intervention: A Secondary Analysis of the OPT-PEACE Randomized Clinical Trial. *JAMA Netw Open* 2023; 6(11):e2343219.
<https://doi.org/10.1001/jamanetworkopen.2023.43219>
11. Rodés-Cabau J, Masson JB, Welsh RC, Garcia Del Blanco B, Pelletier M, Webb JG, *et al.* Aspirin Versus Aspirin Plus Clopidogrel as Antithrombotic Treatment Following Transcatheter Aortic Valve Replacement With a Balloon-Expandable Valve: The ARTE (Aspirin Versus Aspirin + Clopidogrel Following Transcatheter Aortic Valve Implantation) Randomized Clinical Trial. *JACC Cardiovasc Interv* 2017; 10(13):1357-65.
<https://doi.org/10.1016/j.jcin.2017.04.014>
12. Syam AF, Simadibrata M, Wanandi SI, Hernowo BS, Sadikin M, Rani AA. Gastric ulcers induced by systemic hypoxia. *Acta Med Indones* 2011; 43(4):243-8.
13. Langsted A, Nordestgaard BG. Smoking is Associated with Increased Risk of Major Bleeding: A Prospective Cohort Study. *Thromb Haemost* 2019; 119(1):39-47.
<https://doi.org/10.1055/s-0038-1675798>
14. Li LF, Chan RLY, Lu L, Shen J, Zhang L, Wu WKK, *et al.* Cigarette smoking and gastrointestinal diseases: the causal relationship and underlying molecular mechanisms (review). *Int J Mol Med* 2014; 34(2):372-80.
<https://doi.org/10.3892/ijmm.2014.1786>