FUTURITY Medicine

Citation article: Kamri, A. M., Utami, A. N., Hasnawati, A., Avifa, S., Raissa, F., Amirah, S., Sukmawati, Purnamasari, V., Asmaliani, I. Comparison of the Safety Effects of Antiplatelets on the Kidneys in Patients with Vascular Disease. *Futur Med [Internet].* 2024;3(2): 14-20. Available from: https://doi.org/10.57125/FEM.2024.06.30.02

Comparison of the Safety Effects of Antiplatelets on the Kidneys in Patients with Vascular Disease

Andi Maulana Kamri [1*], Atikah Nur Utami [2], Andi Hasnawati [3], Serly Avifa [4], Fadhilah Raissa [5], Sitti Amirah [6], Sukmawati [7], Vina Purnamasari [8], Ira Asmaliani [9]

[1,6,7,9] Faculty of Pharmacy, Biopharmacy and Pharmacology Laboratory, Universitas Muslim Indonesia, Indonesia
[8] Faculty of Pharmacy, Pharmaceutical Laboratory, Universitas Muslim Indonesia, Indonesia
[2,3,4,5] Faculty of Pharmacy, Bachelor's Degree, Universitas Muslim Indonesia, Indonesia

Abstract

Aims: Most vascular disorders fall under the category of inflammatory diseases because they gradually harm blood vessels, disrupting the normal flow of blood to and from vital organs. The purpose of this research was to determine the potential dangers to kidney health associated with acetylsalicylic acid and clopidogrel treatment in patients with vascular diseases.

Methodology: A cross-sectional research design was employed in the study, as well as retrospective data collection methods on medical records, and purposive sampling-based data sampling methodologies.

Results: The study's findings indicated that there was no significant correlation between the use of antiplatelets and the risk of developing kidney disorders. It is rather, a patient's lifestyle, use of medications that increase the risk of renal GFR, and co-occurring diseases that may impair blood flow in the renal afferen can all increase their risk of developing a renal disorder with p-value <0.05. Nevertheless, the prolonged use of medication also plays a significant role in kidney function. The study's results indicate that renal problems are not attributed to the usage of antiplatelet drugs such as clopidogrel and acetylsalicylic acid.

Scientific Novelty: Several using antiplatelet for indicated cardiovascular disease such us, atherosclerosis, plaque formation, endothelial dysfunction, and blockage or damage to the vascular endotelial matrix are all symptoms of vascular disease, a progressive inflammatory illness, it's frequently associated with the risk of kidney disorders. The use of antiplatelet will enlarge the afferent blood vessels.

Conclusion: Instead, factors such as a patient's lifestyle, the severity of their condition, and their medical history could have a more significant impact on the likelihood of developing kidney dysfunction.

Keywords: antiplatelet; clopidogrel; acetylsalicylic acid; renal impairment; risk adverse event.

Received: December 5, 2023
Revised: December 12. 2023
Accepted: April 3, 2024
Published: April 20, 2024

Introduction

Non-communicable diseases (NCDs) pose a significant worldwide risk to human life, health, and sustainable development in countries with low and intermediate incomes [1, 2]. As per the World Health Organisation (WHO), nearly 36 million deaths occur annually due to non-communicable diseases. These diseases are caused by various

* **CONTACT:** andimaulanakamri@gmail.com
DOI: https://doi.org/10.57125/FEM.2024.06.30.02

risk factors that are widespread and interconnected through a complicated cause-and-effect system [3,4]. Vascular disease is a significant non-communicable condition that has a reasonably high occurrence of illness and death. Vascular disease is a medical disorder that disrupts the balanced blood circulation from the heart and organs. According to data from RISKESDAS in 2018, it was discovered that the number of vascular disease cases in Indonesia significantly increased, reaching a total of 2,784,064 instances. The increase in occurrences in recent decades can be attributed to a raised risk of factors for the disease, such as advancing age, lifestyle choices, and complications arising from concurrent conditions including hypertension and diabetes mellitus [5-8].

Pharmacological therapy is employed to manage and improve the quality of life for patients diagnosed with vascular disease. This involves the administration of both temporary and long-term anticoagulant therapy, which functions by inhibiting platelet aggregation and the coagulation cascade. Clopidogrel is an oral antiplatelet medication that has received approval from the Food and Drug Administration (FDA) since the 1950s. Clopidogrel continues to be the primary treatment for vascular illnesses, such as thromboembolism and stroke, and for preventing blood clot dissolution in patients with atrial fibrillation, prosthetic heart valves, and myocardial infarction. Despite the availability of approved oral anti-platelet aggregation therapy choices (DOAC) such dabigatran and apixaban, the usage of warfarin remains prevalent in healthcare facilities [9,10]. The American Heart Association and Society of Vascular Surgery recommend a daily dose of acetylsalicylic acid ranging from 81 to 325 mg as a means of treatment and prevention of vascular disease. Although other anti-platelet drugs, such as clopidogrel, have shown almost the same activity, acetylsalicylic acid is still one of the treatment therapies for the population of patients with this disease. The relatively low cost and ease of acquisition in healthcare are the primary reasons for the predominant use of acetylsalicylic acid over other antiplatelet drugs [11,12,13].

The long-term use of non-steroidal anti-inflammatory medicines (NSAIDs) significantly impacts the kidney function, particularly in individuals with vascular disease. In a recent study conducted by Takayuki Katsuno (2021), it was found that the use of non-steroidal anti-inflammatory drugs (NSAIDs) could lead to an elevated risk of kidney disorder. This risk was particularly high in individuals who have been using NSAIDs for an extended period of time and had a history of prior kidney failure [14,15]. Several studies have been conducted in several countries, including Indonesia, in order to assess the efficacy of using clopidogrel and acetylsalicylic acid [16,17,18]. However, the primary focus of these research was to assess the dosage concerning International Normalized Ratio (INR) control. On the other hand, studies conducted in Indonesia had a limited sample size of patients. Further research is required to compare the impact on the kidneys caused by the administration of this medication. This research also aimed to identify any associated clinical symptoms as well as to conduct laboratory tests. The objective is to gain a comprehensive understanding of the most effective use of clopidogrel and acetylsalicylic acid, while minimising the potential harm to the kidneys. This is particularly important for patients with vascular disease who rely on long-term treatment with both of these drugs, potentially for the rest of their lives.

Research Methodology

General Background

This study adopted an analytical observational approach with a retrospective cross-sectional research design. The subjects were collected using secondary medical record data and the history of drug use of vascular disease patients who received anticoagulant and antiplatelet therapy and met the inclusion criteria between January and December 2023. The used medical record data included patient identity, clinical characteristics, blood pressure, medical history, and drug use history, including the name and dosage of the drug. Subjects were used as samples for research and observed for a year. The variables that were the subject of the study were parameters of decreased kidney function and the occurrence of vascular disease. Observed cases of vascular disease included hypertension, stroke, congestive heart failure, atherosclerosis, and diabetes mellitus. The study has limited time scope because it can't track the history of anti-platelet users any further and cannot track the patient's future development from the time of the study.

Sample / Participants / Group

The inclusion criteria consisted of adults aged over 18 who have been diagnosed with vascular disease, as described previously, and are undergoing anticoagulant and antiplatelet therapy while also undergoing a comprehensive blood test. Patients with incomplete medical records, those who passed away prior to the conclusion of the monitoring period, pregnant women, patients undergoing kidney transplantation or having late-stage kidney disease during the sampling period, patients diagnosed with cancer, or those undergoing chemotherapy are excluded from the study. The sampling technique was carried out purposefully based on the calculation of the population suffering from vascular disease in the province of South Sulawesi. 142 patients were chosen. The total sample included in this study was 89 patients. The group of anticoagulants used in the study was clopidogrel, while the group of antiplatelet drugs used in this study was acetylsalicylic acid.

Data Analysis

The data analysis was statistically performed using bivariate and multivariate analysis to compare variable significance in statistical terms so that meaningful comparisons could be obtained between the two compared anticoagulant and antiplatelet drugs. In bivariate analysis, the chi-square analysis method was used to analyse the nominal data of the relationship between clopidogrel and salicylic acetylic acid use in renal patients with vascular disease. In addition, chi-square analysis was applied to the analysis of role variables such as gender, age, and comorbidity.

Research Results

Research

The vascular disease patients included in the study are presented in table I. 47% of patients are male, and 53% are female. The gender and age characteristics of patients in both groups of studies found no statistically significant differences (p>0,05).The presentation of clopidogrel patients in this study was 18 patients, while the presentation of aspirin patients was 71 patients. As for vascular disease patients using clopidogrel therapy, with high blood pressure patients were predominantly presented at 33%, followed by congestive heart disease patients at 27%. Meanwhile, vascular disease patients using aspirin anti-platelet therapy were dominated by patients with congestible heart disease, with a presentase of 32%, following hypertensive patients at 31%.

Table 1. Characteritics of Research Subject based on Gender and Age (n=89)

Variable	Karakteristik	Total n = 89 (%)	Jumlah	
			Clopidogrel n = 18 (%)	Acetylsalicylic acid n = 71(%)
Sex	Man	42 (47)	7 (39)	35 (49)
	Woman	47 (53)	11(61)	36 (50)
Classified patient	< 60 years old	43 (48)	9 (50)	34 (47)
	> 60 years old	46 (51)	9 (50)	37 (52)

The analysis of treatment characteristics for patients with vascular diseases, considered one of the dependent variables, was conducted using the bivariate chi-square method. Vascular disease patients with clopidogrel therapy in Ibnu Sina Makassar Hospital and in RSUD Labuang Baji Makassar ranged from 17 to 71 patients, with a long majority of therapy over 7 days. Vascular disease patients in this study generally received several therapies in addition to anticoagulants and antiplatelet inhibitors, namely beta, CCB dihydropyridine, digoxin, statins, metformin, sulfonylurea, proton pump inhibitors (PPI), insulin, diuretics, amiodaron, and anticholesterol drugs. In addition, vascular disease patients receiving clopidogrel and acetylsalicylic acid therapy were dominated by patients with a history of cardiovascular disease ranging from 84 people.

Using a multivariate analysis with a sample significance threshold of 5%, the multivariate analysis examines the impact of the glomerulus and creatinine filtering the rate variables as indicators of kidney injury. If there was a significant difference between the variables based on kidney loss (p value < 0.05), the statistical test findings were considered meaningful or connected. The outcomes of the study's multivariat analysis are as follows. In the multivariate analysis, the influence of the glomerulus and creatinine filtering rate variables as parameters of kidney damage was analysed using a multivariate analysis with a sample significance level of 5%. The statistical test results were stated to be meaningful or related if the p value <0.05 means there was a significant difference between the variables depending on kidney loss.

Table 2. Multivariate analysis of the relationship between the dependent variable and glomerular filtration rate.

Dependent Variable	Mean	p-value
Ras	0.81	0.966
Blood pressure	0.148	0.006*
Lifestyle	0.151	0.045*
Therapy	0.179	0.221
Time exposure	0.47	0.01*
Drugs history	0.123	0.03*
Comorbidity	0.012	0.035*

* is indicated significant relation

According to the table 2, 71 patients were treated with aspirin, 50 of whom were indicated to have reduced kidney function characterised by glomerulus filtration rate < 60 (mg/dL). Meanwhile, 17 patients received clopidogrel therapy, 14 had reduced renal function. In the statistical analysis of multivariate it is known that the p-value value (p > 0,05) means no significant or significant difference between the therapeutic characteristics of either patient therapy therapy clopidogrel and salicylic acetylic acid treatment of patients against the rate of glomerulus and serum creatinine filtration as one of the parameters of kidney damage. According to a cohort study of the clinical picture of the kidney of a vascular patient conducted by Chiu, showing that the use of NSAIDs may increase the risk of kidney disease in elderly patients and comorbid chronic disease, regardless of its class and selectivity in the treatment of vascular disease [8]. The study analysed the influence of the history of the disease on the rate of glomerulus and creatinine filtration with a multivariate analysis to evidence if there was an influence on the glomerulus filtration rate. According to table 2, 82 patients with a history of cardiovascular disease, 62 of whom were indicated to have reduced kidney function with a glomerulus filtration rate of < 60 (mg/dL). Meanwhile, 4 patients with concomitant non-cardiovascultural disease, 2 of them indicated a reduced renal function. In the multivariate analysis it was stated that the p-value (p > 0.05) means no significant or significant difference between the history of comorbid disease of the patient with respect to the rate of glomerulus filtration and serum creatinine of the vascular patient at Ibnu Sina Hospital and RSUD Labuang Baji Makassar. Patient with uncontrol blood pressure having indicated for reduce GFR like statistical result showed p-value 0.006. This is because constriction in the afferent renal arteriole can lead to increased pressure, potentially reducing blood supply to the glomerulus.

It was observed that patients with unhealthy lifestyles, such as alcohol and cigarette consumption, are at risk of experiencing a reduction in GFR. The data indicate that patients with such lifestyles are more likely to experience a decrease in GFR. Patient with history using drug induced renal failure like diuretic, sulfonylurea, CCB, and statin have potentially risk compared to just using antiplatelet, and we can see with analytic p-value 0.03. Patient with comorbid hypertension, CHF, and stroke is more have risk occur Disorders of data connectivity mainly to the kidneys, so when compared to the use of drugs, the disease is more likely to cause renal disorders.

Discussion

In studies examining the effects of non-steroidal anti-inflammatory drugs (NSAIDs) on kidney function, it has been found that NSAID users who undergo longer treatment durations face an elevated risk of kidney disorders. Moreover, this risk is heightened in patients with a history of renal failure [18,19]. Therefore, the study undertook an analysis of the long-term impact of therapy and the utilization of treatment regimens on glomerular filtration rate and serum creatinine levels through multivariate analysis. This aimed to determine whether there was a sustained effect of treatment and medication usage on kidney damage parameters [20, 21, 22].

During the treatment period of less than 7 days of 29 patients, 24 of whom were indicated to have reduced kidney function characterised by glomerulus filtration rate < 60 (mg/dL). The multivariate test results showed a p-value of (p > 0.05) which means that there was no significant influence between the duration of therapy on the rate of glomerular filtration and the serum creatinine of the vascular patient. In the use of therapeutic therapy, the results of multivariate analysis showed a p-value of (p > 0.05) which means that there was no significant influence between the history of drug use on the rate of glomerulus filtration and vascular creatinine of the patient. Study data on chronic kidney failure patients treated in RSUP hospital Prof. Dr. R. D. Kandou Manado showed that 52% of patients were active smokers. Smoking has been proven based on several statistical trials to have a significant link to the incidence of chronic kidney failure. A study conducted on the analysis of risk factors for chronic kidney failure in the hemodialysis unit of Dr. Moerwadi Hospital showed data that there was a significant relationship between the history of smoking and the incidence of chronic renal failure. Therefore, an analysis of life patterns such as smoking and alcohol consumption on glomerular filtration rates was carried out with crosstab and chi square analysis to find out if there was an influence of non-living pattern on the glomerulus filtration rate. It is known that 86 patients with a lifestyle that is not at risk of kidney disease, 63 of whom were indicated to have reduced kidney function characterised by glomerulus filtration rate < 60 (mg/dL). The multivariate test results showed a p-value of (p > 0.05) which means there was no significant influence between life patterns on the patient's vascular glomerulus filtration rate [16,20]. Clopidogrel is a widely used anti-platelet drug. Clopidogrel works by blocking the P2Y12 component of the ADP receptor in the thrombocytes. It is a thrombotic aggregation inhibitor that has a good effect and is often used in patients with mild strokes to prevent strokes. Clopidogrel has a different antiplatelet effect on each patient. Clopidogrel is a slow-working product. The usual dose is 75 mg/day. The effects of Clopidogrel are visible from the first day of use to 1 year of use in reducing cerebrovascular incidence. In addition to its effective effects, Clopidogrel also causes side effects such as bleeding, discomfort in the gastrointestinal tract, diarrhoea, and rash. The oral dose of clopidogrel is 75 mg/day. The ACCF/AHA report for peripheral artery disease recommends clopidogrel as a substitute for aspirin or concomitant aspirin for those who do not experience elevated blood pressure and bleeding but are at high cardiovascular risk [8]. For Stemi's disease, the initial dose of 600mg was then continued with 75 mg/day, but with the note that the 600mg dose is only given if in fibrinolytic treatment. According to research, thrombocyte inhibition with clopidogrel treatment over the last 3 months has been effective in reducing

accumulation and kidney fibrosis. At therapeutic doses, elimination takes place rapidly through non-renal mechanisms. At very high doses, kidney elimination may be more important [23, 24, 25]. However, dose adjustment remains unnecessary for patients with renal impairment.

Conclusions and Implications

This study showed that there was no correlation between the incidence of renal impairment in patients and their use of antiplatelets. The risk factors for chronic kidney disease (CKD) were the lifestyle factors, blood pressure uncontrol, drug use history, and history of cardiovascular disease.

Declarations

Author Contributions

Conceptualization, X.X. and Y.Y.; methodology, X.X.; software, X.X.; validation, X.X., Y.Y. and Z.Z.; formal analysis, X.X.; investigation, X.X.; resources, X.X.; data curation, X.X.; writing–original draft preparation, X.X.; writing–review and editing, X.X.; visualization, X.X.; supervision, X.X.; project administration, X.X.; funding acquisition, Y.Y. All authors have read and agreed to the published version of the manuscript.

Author Contributions

Conceptualisation, Andi Maulana Kamri; methodology, Andi Maulana Kamri; software, Andi Maulana Kamri; validation, Sitti Amirah, and Vina Purnamasari; formal analysis, Sukmawati; investigation, Atikah Nur Utami, and Andi Hasnawati; resources, Ira Asmaliani; data curation, Serly Avifa; writing–original draft preparation, Atikah Nur Utami and Fadhilah Raissa; writing–review and editing, Andi Maulana Kamri; visualization, Sitti Amirah; supervision, Andi Maulana Kamri, Sitti Amirah, Vina Purnamasari, Sukmawati, and Ira Asmaliani; project administration, Vina Purnamasari; funding acquisition, Andi Maulana Kamri. All authors have read and agreed to the published version of the manuscript.

Data Availability Statement

Data available upon request due to constraints such as privacy or ethical considerations. Interested parties can obtain the data presented in this research by contacting the corresponding author upon request. The statistics are not publicly available due to constraints such as privacy or ethical issues. Data requests will be evaluated individually to ensure that all possible hazards and ethical concerns are adequately addressed.

Funding

No Funding

Acknowledgements

Thanks to Universitas Muslim Indonesia, Ibnu Sina Hospital, Tadjuddin Chalid Hospital, and Labuang Baji Hospital in Makassar for help research data retrieval.

Conflicts of Interest

The author affirms the absence of any conflicting interests in relation to the publishing of this article. Furthermore, the writers have diligently adhered to ethical considerations, such as plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publishing and/or submission, and redundancy.

References

1. Liu S, Chen Z, Han L, Dong W, Li H, Koplan J, et al. Integrated multisectoral non-communicable disease prevention and control in China: A review of agencies and policies. J Glob Health [Internet]. 2020;10(2). Available from: http://dx.doi.org/10.7189/jogh.10.020304

2. Marchewka Z, Szymczak A, Knysz B. Comorbidities as risk factors of chronic kidney disease in HIV-infected persons. Postepy Hig I Med Doswiadczalnej [Internet]. 2015 Dec 16 [cited 2024 Apr 15];69:1364-70. Available from: https://doi.org/10.5604/17322693.1186343

3. Sudayasa IP, Rahman MF, Eso A, Jamaluddin J, Parawansah P, Alifariki LO, et al. Deteksi Dini Faktor Risiko Penyakit Tidak Menular Pada Masyarakat Desa Andepali Kecamatan Sampara Kabupaten Konawe. jceh [Internet]. 2020 Mar. 1 [cited 2024 Apr. 15];3(1):60-6. Available from: https://jceh.org/index.php/JCEH/article/view/37

4. Lu C-H, Fang C-W, Chen H-M, Fang Y-P, Fang C-T, Huang Y-B, et al. Prescribing patterns of coronary artery aneurysm in Taiwan. BMC Cardiovasc Disord [Internet]. 2019;19(1):188. Available from: http://dx.doi.org/10.1186/s12872-019-1172-6

5. Schrottmaier WC, Mussbacher M, Salzmann M, Assinger A. Platelet-leukocyte interplay during vascular disease. Atherosclerosis [Internet]. 2020;307:109–20. Available from: http://dx.doi.org/10.1016/j.atherosclerosis.2020.04.018

6. Shi J, Yang Y, Cheng A, Xu G, He F. Metabolism of vascular smooth muscle cells in vascular diseases. Am J Physiol Heart Circ Physiol [Internet]. 2020;319(3):H613–31. Available from: http://dx.doi.org/10.1152/ajpheart.00220.2020

7. Mondelo García C, Martínez Roca C, Rueda Núñez F, Martín Herranz MI. ¿Cuál es la dosis óptima de clopidogrel en pacientes pediátricos? An Pediatr (Barc) [Internet]. 2019;90(4):219–23. Available from: http://dx.doi.org/10.1016/j.anpedi.2018.05.020

8. Chiolero A, Burnier M, Maillard MP. Cardiovascular hazard of selective COX-2 inhibitors: myth or reality? Expert Opin Drug Saf [Internet]. 2002;1(1):45–52. Available from: http://dx.doi.org/10.1517/14740338.1.1.45

9. D.A Ningrum V, Sufiyah S, Dyah Widyastuti I, Sufriyanto Yusuf B, Dullah W. Bleeding Incidence in Patients Administered with Warfarin at Secondary Hospitals in Yogyakarta Province. Indonesian J Pharm [Internet]. 2020Sep.30 [cited 2024Apr.15];31(3):217-28. Available from: https://jurnal.ugm.ac.id/v3/IJP/article/view/814

10. Peres G, Mariana M, Cairrão E. Pre-eclampsia and eclampsia: An update on the pharmacological treatment applied in Portugal. J Cardiovasc Dev Dis [Internet]. 2018;5(1):3. Available from: http://dx.doi.org/10.3390/jcdd5010003

11. Khan H, Kanny O, Syed MH, Qadura M. Aspirin resistance in vascular disease: A review highlighting the critical need for improved point-of-care testing and personalized therapy. Int J Mol Sci [Internet]. 2022;23(19). Available from: http://dx.doi.org/10.3390/ijms231911317

12. Zheng Z, Ma T, Lian X, Gao J, Wang W, Weng W, et al. Clopidogrel reduces fibronectin accumulation and improves diabetes-induced renal fibrosis. Int J Biol Sci [Internet]. 2019;15(1):239–52. Available from: http://dx.doi.org/10.7150/ijbs.29063

13. Højlund M, Lund LC, Herping JLE, Haastrup MB, Damkier P, Henriksen DP. Second-generation antipsychotics and the risk of chronic kidney disease: a population-based case-control study. BMJ Open [Internet]. 2020;10(8):e038247. Available from: http://dx.doi.org/10.1136/bmjopen-2020-038247

14. Katsuno T, Togo K, Ebata N, Fujii K, Yonemoto N, Abraham L, et al. Burden of renal events associated with nonsteroidal anti-inflammatory drugs in patients with osteoarthritis and chronic low back pain: A retrospective database study. Pain Ther [Internet]. 2021;10(1):443–55. Available from: http://dx.doi.org/10.1007/s40122-020-00233-w

15. Luo P-J, Lin X-H, Lin C-C, Luo J-C, Hu H-Y, Ting P-H, 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 [Internet]. 2019;118(5):939–44. Available from: http://dx.doi.org/10.1016/j.jfma.2018.10.007

16. Semakula JR, Mouton JP, Jorgensen A, Hutchinson C, Allie S, Semakula L, et al. A cross-sectional evaluation of five warfarin anticoagulation services in Uganda and South Africa. PLoS One [Internet]. 2020;15(1):e0227458. Available from: http://dx.doi.org/10.1371/journal.pone.0227458

17. Roberge S. The role of aspirin dose on the prevention of preeclampsia and fetal growth restriction: systematic review and meta-analysis [Internet]. Vol. 216, American Journal of Obstetrics and Gynecology. 2017. p. 110–20. Available from: https://api.elsevier.com/content/article/eid/1-s2.0-S0002937816307839

18. Kamri AM, Ikawati Z, Hashim R, Rahmawati F. An evaluation of the relationship between the occurrence of chronic kidney disease and the use of NSAIDs. Bali Med J. 2023;12(1):153-7. Available from: https://doi.org/10.15562/bmj.v12i1.3814

19. Roberge S, Bujold E, Nicolaides KH. Aspirin for the prevention of preterm and term preeclampsia: systematic review and metaanalysis. Am J Obstet Gynecol [Internet]. 2018;218(3):287-293.e1. Available from: http://dx.doi.org/10.1016/j.ajog.2017.11.561

20. Katzung BG, Masters SB, Trevor AJ. Farmakologi Dasar & Klinik. Vol. 2. Edisi 12. Jakarta: Penerbit Buku Kedokteran EGC; 2014. Available from: https://laser.umm.ac.id/catalog-detail-copy/160002327/

21. Ikeme JC, Pergola PE, Scherzer R, Shlipak MG, Benavente OR, Peralta CA. Post hoc analyses of randomized clinical trial for the effect of clopidogrel added to aspirin on kidney function. Clin J Am Soc Nephrol [Internet]. 2017;12(7):1040–7. Available from: http://dx.doi.org/10.2215/cjn.00100117

22. Kitchens BP, Snyder RJ, Cuffy CA. A Literature Review of Pharmacological Agents to Improve Venous Leg Ulcer Healing. Wounds. 2020 Jul;32(7):195-207. PMID: 33166265.

23. Eikelboom JW, Hirsh J, Spencer FA, Baglin TP, Weitz JI. Antiplatelet drugs. Chest [Internet]. 2012;141(2):e89S-e119S. Available from: http://dx.doi.org/10.1378/chest.11-2293

24. LeFevre ML. Low-dose aspirin use for the prevention of morbidity and mortality from preeclampsia: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med [Internet]. 2014;161(11):819–26. Available from: https://api.elsevier.com/content/abstract/scopus_id/84919499487

25. Xu L, Li C, Zhao L, Zhou B, Luo C, Man X, et al. Acute kidney injury after nephrectomy: a new nomogram to predict postoperative renal function. BMC Nephrol [Internet]. 2020;21(1):181. Available from: http://dx.doi.org/10.1186/s12882-020-01839-0