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Research Article

Study of Utilization of Antiplatelet Agents in Coronary Heart Disease Patients in Private Hospital in Surabaya

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ABSTRACT

Antiplatelet is the most commonly drug used as secondary prevention for Coronary Heart Disease (CHD). The aim of this study was to determine the profile of the use of antiplatelet related with its efficacy and side effects. Observational methods with *cross sectional* approach for 3 months follow up was used, a descriptive analysis carried out at the private hospital in Surabaya. Results from this study: aspirin 80 mg was the most prescribed antiplatelet in patients with the incidence of ischemic events 9%. Higher ischemic events also seen in patients with hypertension, dyslipidemia, and Diabetes Mellitus. Bleeding and gastrointestinal disturbance as side effects occurred in 4 patients who used aspirin as antiplatelet, and based for Naranjo scale can be concluded as possible adverse drug reaction.

Keywords: Coronary Heart Disease, Antiplatelet , *Ischemic events, Bleeding*

I. BACKGROUND

Data from Basic Health Research (RISKESDAS) in 2018 showed the prevalence of cardiovascular diseases in Indonesia , such as heart disease prevalence approximately 1.5%, 8.36% hypertension, and stroke was 10.9%. In East Java Province, the prevalence of heart disease patient was 1.5%, hypertension patients were 8.01%, and stroke patients were 12.4%.

One of the common therapies for the management of Coronary Heart Disease (CHD) is antiplatelet. Antiplatelet is a drug used to prevent platelet aggregation in the blood. Platelet aggregation can cause blood coagulation that triggers a heart attack (Kurniadi H,

2015). Antiplatelet therapy is an important therapy for *secondary prevention* of *coronary artery disease* accompanied by lifestyle modification and controlling cardiovascular risk factors (Pilgrim T, 2014). Besides being used for *coronary artery disease* therapy , antiplatelet can also be used in patents with PCI therapy (Tayeb HM *et al* , 2011). Antiplatelet drugs can protect against the incidence of myocardial infarction, stroke, and cardiovascular death in patients with a history of previous vascular events or risk factors for cardiovascular disease (Hankey GJ and Eikelboom JW, 2003). Oral antiplatelet agents for *secondary prevention* include *cyclooxygenase* 1 *inhib itors* namely aspirin and P2Y12 *inhibitors* that depend on ADP, such as clopidogrel, ticagrelor, and prasugrel.(Pilgrim T, 2014).

Beyond its efficacy in CHD, antiplatelet also have main side effects. Common side effects from antiplatelets is bleeding which can be seen by looking at symptoms such as bleeding in the gums, nasal bleeding and bruising (Gregg D, 2003). In addition, antiplatelet therapy also causes gastrointestinal bleeding, especially in elderly patients. Reported risk factors for gastrointestinal bleeding include advance age, female sex, major organ dysfunction (heart, lung, or liver), diabetes, hypertension, positive results for *Helicobacter pylori infection* and haemostatic abnormalities (Yasuda H, 2015). The use of antiplatelet agents combined with anticoagulants, *Non-Steroidal Anti-Inflammatory (NSAID)* can also increase the risk of bleeding. *Proton Pump Inhibitors* (PPI) can be used to reduce the risk of gastrointestinal bleeding can be used together with (Rodriguez LA., *Et al.* 2016).

Based on the data above, research will be conducted on the use of antiplatelet to see the incidence of ischemic event and side effects of bleeding in outpatient coronary heart disease patients in hospitals.

II. METHODS

This study was an observational study with a *cross sectional* approach in which variable data retrieval was carried out at one time at the same time by using descriptive analysis.

This research was conducted in a private hospital in Surabaya.

A. Population and Sample

The population in this study were all outpatient coronary heart disease patients at cardiology polyclinic. at a hospital in Surabaya. Inclusion criteria for sample in this study were: patients were willing to take part in the study, using

antiplatelet therapy, did not have hearing sensory problems.

B. Method of collecting data

This research was started by giving *informed consent* to provide information about what should be done to participate in this research, patient have rights to decline any data if they don't want. Furthermore , patient data collection is obtained through the patient's medical record. The record includes name, age, gender, weight, height, comorbidities condition and drugs used. Ischemic events and side effects obtained from patient medical record and patient's interview.

C. Data analysis

Data obtained from this study will be analyzed using descriptive statistical techniques . The results obtained in the form of tables , diagrams and percentages.

III. RESULTS AND DISCUSSION

Ischemic events difference can be seen based on antiplatelet (Table I) , gender (Table II), age (Table III) , comorbidic conditions (Table IV). Incidence of side effects of antiplatelet therapy in patients can be described in Table V.

Table I. Cross Tabulation Between Antiplatelet and Ischemic Events

Antiplatelet Therapy	Ischemic Events	Without ischemic events	Total
aspirin 80 mg	6 (9%)	31 (45%)	37 (54%)
clopidogrel 75 mg	-	14 (20%)	14 (20%)
aspirin 80 mg + clopidogrel 75 mg	2 (3%)	12 (17%)	14 (20%)
aspirin 80 mg switch clopidogrel 75 mg	-	4 (6%)	4 (6%)
Total	**8 (12%)**	**61 (88%)**	**69 (100%)**

Based on Table I above, most commonly used of antiplatelet therapy was aspirin 80 mg from February-April 2018 for 37 (54%) patients. 45% patients didn't experienced any ischemic events with Aspirin 80 mg during 3 months follow up. Clopidogrel is used by 20% patients as single antiplatelet therapy. Based on guideline recommendations for Chronic Coronary Syndrome, Aspirin is the first line therapy for antiplatelet in CCS patients who didn't get any Acute Coronary Syndrome or undergone PCI procedure. In addition there were 4 (5%) patients who switched 80 mg aspirin to 75 mg clopidogrel, this was because the patient had gastrointestinal complaints. The total number of patients using combination of dual

antiplatelet therapy (80mg aspirin + 75 mg clopidogrel is 14 (20%) patients, this combination can reduce the incidence of chest pain by 12 (17%) patients .

Table II. Cross Tabulation Between Antiplatelet, Ischemic Events and Gender

Antiplatelet Therapy based on Gender	Ischemic Events	Without ischemic events	Total
aspirin 80 mg	**6 (9%)**	**31 (45%)**	**37 (54%)**
Male	3 (4%)	23 (33%)	26 (38%)
women	3 (4%)	8 (12%)	11 (16%)
clopidogrel 75 mg	**-**		
Male	-	7 (10%)	7 (10%)
women	-	7 (10%)	7 (10%)
aspirin 80 mg + clopidogrel 75 mg	**2 (3%)**	**12 (17%)**	**14 (20%)**
Male	2 (3%)	11 (16%)	13 (19%)
women	-	1 (1%)	1 (1%)
aspirin 80 mg *switch* c lopidogrel 75 mg	**-**	**4 (6%)**	**4 (6%)**
women	-	4 (6%)	4 (6%)
Total	**8 (12%)**	**61 (88%)**	69 (100%)

Based on table II, we can see that there were no difference between male and female in incidence of ischemic events. According to Ittaman SV in 2014 it was said that the use of aspirin was primarily aimed at the sex of men compared to women. The reasons for differences in the effects of aspirin therapy by sex are currently unknown, but evidence suggests that there may be some biological basis for these differences.

Special characteristic for women is the influence of their hormonal status on CHD. In comparison with men of a similar age and postmenopausal women suggesting that endogenous estrogens have a protective effect on the development of CHD. Estrogen affect the atheroschlerotic process through a variety of mechanism. It has been reported to have a lowering effect on total cholesterol and LDL, lipoprotein, and homocystein levels. HDL levels are increased and postprandial lipid metabolism improved by estrogens. Moreover, estrogens have an acute vasodilatory effect on the vessel wall and an atheroprotective effect involving inhibition of smooth muscle cell proliferation (Lennep et al, 2002). But after postmenopause, the risk to suffering from CHD is equal between men and women, because of the decrease in women estrogen production.

The relationship of antiplatelet therapy with ischemic events based on age can be seen in Table III. Patients aged 65-69 years were the highest age using aspirin 80mg, 10 (14%) patient did not experience ischemic events. Aspirin provides better clinical outcomes at age ≥ 65 years by reducing mortality (Hwang IC, Jeon JY, *et al*¸ 2015).

Table III. Cross Tabulation Between Antiplatelet, Age and Ischemic Events

Antiplatelet therapy based on age	Ischemic Events	Without ischemic events	Total
aspirin 80 mg	**6 (9%)**	**31 (45%)**	**37 (54%)**
40-44 y.o	-	1 (1%)	1 (1%)
45-49 y.o	-	1 (1%)	1 (1%)
50-54 y.o	1 (1%)	2 (3%)	3 (4%)
55-59 y.o	2 (3%)	5 (7%)	7 (10%)
60-64 y.o	1 (1%)	6 (9%)	7 (10%)
65-69 y.o	-	10 (14%)	10 (14%)
70-74 y.o	1 (1%)	3 (4%)	4 (6%)
≥ 75 y.o	1 (1%)	3 (4%)	4 (6%)
clopidogrel 75 mg	**-**		
40-44 y.o	-	2 (3%)	2 (3%)
45-49 y.o	-	1 (1%)	1 (1%)
50-54 y.o	-	1 (1%)	1 (1%)
55-59 y.o	-	1 (1%)	1 (1%)
60-64 y.o	-	4 (	4
65-69 y.o	-	1 (1%)	1 (1%)
70-74 y.o	-	1 (1%)	1 (1%)
≥ 75 y.o	-	1 (1%)	1 (1%)
65-69 y.o	-	2 (3%)	2 (3%)
aspirin 80 mg + clopidogrel 75 mg	**2 (3%)**	**12 (17%)**	**14 (20%)**
45-49 y.o	1 (1%)	2 (3%)	3 (4%)
50-54 y.o	1 (1%)	1 (1%)	2 (3%)
60-64 y.o	-	2 (3%)	2 (3%)
65-69 y.o	-	4 (6%)	4 (6%)
70-74 y.o	-	2 (3%)	2 (3%)
35-39 y.o	-	1 (1%)	1 (1%)
aspirin 80 mg switch clopidogrel 75 mg	**-**	**4 (6%)**	**4 (6%)**
55-59 y.o	-	1 (1%)	1 (1%)
60-64 y.o	-	1 (1%)	1 (1%)
70-74 y.o	-	1 (1%)	1 (1%)
≥ 75 y.o	-	1 (1%)	1 (1%)
Total	**8 (12%)**	**61 (88%)**	**69 (100%)**

Table IV. Cross Tabulation Between Antiplatelet, Comorbid conditions and Ischemic Events

Antiplatelet Therapy Based on Comorbid conditions	Ischemic Events	Without ischemic events	Total
aspirin 80 mg	**6 (9%)**	**31 (45%)**	**37 (54%)**
DCFC + HT + DM	1 (1%)	-	1 (1%)
Moderate AF + DCFC	-	1 (1%)	1 (1%)
CKD + DM	1 (1%)	-	1 (1%)
CVA + HT + DM + dyslipidemia	-	1 (1%)	1 (1%)
DCFC + HT + dyslipidemia	-	1 (1%)	1 (1%)
DM	-	2 (3%)	2 (3%)
DM + CKD + DCFC	-	1 (1%)	1 (1%)
DM + DCFC	2 (3%)	2 (3%)	4 (6%)
DM + hyperglycemia + HT	-	1 (1%)	1 (1%)
DM + HT	2 (3%)	2 (3%)	4 (6%)
DM + HT + DCFC	1 (1%)	1 (1%)	2 (3%)
HT	-	4 (6%)	4 (6%)
HT + AV block	-	1 (1%)	1 (1%)
HT + CKD	-	1 (1%)	1 (1%)
HT + DCFC	-	3 (4%)	3 (4%)
HT + DCFC + CKD	-	1 (1%)	1 (1%)
HT + dyslipidemia	1 (1%)	2 (3%)	3 (4%)
HT + DM + DCFC	-	1 (1%)	1 (1%)
HT + DM + dyslipidemia	-	1 (1%)	1 (1%)
without comorbidities	-	3 (4%)	3 (4%)
clopidogrel 75 mg	**-**		
CKD	-	1 (1%)	1 (1%)
DM	-	1 (1%)	1 (1%)
DM + HT + DCFC	-	2 (2 %)	2 (2 %)
HT	-	2 (2 %)	2 (2 %)
HT + dyslipidemia	-	1 (1%)	1 (1%)
HT + dyslipidemia + hyperuricemia	-	1 (1%)	1 (1%)
HT + hyperuricemia + gastritis	-	1 (1%)	1 (1%)
without comorbidities	-	1 (1%)	1 (1%)
DM + CKD + CVA + dyslipidemia + post MF	-	1 (1%)	1 (1%)
DM + HT	-	1 (1%)	1 (1%)
HT + DCFC	-	1 (1%)	1 (1%)
HT + DCFC + CVA	-	1 (1%)	1 (1%)
aspirin 80 mg + clopidogrel 75 mg	**2 (3%)**	**12 (17%)**	**14 (20%)**
CVA + HT + DCFC	-	1 (1%)	1 (1%)
CVA infarction + hyperuricemia	-	1 (1%)	1 (1%)

Antiplatelet Therapy Based on Comorbid conditions	Ischemic Events	Without ischemic events	Total
DM + CVA + AF post	1 (1%)	-	1 (1%)
DM + HT + dyslipidemia	-	1 (1%)	1 (1%)
HT	-	1 (1%)	1 (1%)
HT + CVA	-	1 (1%)	1 (1%)
HT + CVA + dyspepsia	-	1 (1%)	1 (1%)
HT + DCFC + dyslipidemia	-	1 (1%)	1 (1%)
HT + dysilipidemia + DCFC	1 (1%)	-	1 (1%)
without comorbidities	-	5 (7%)	5 (7%)
aspirin 80 mg *switch* clopidogrel 75 mg	**-**	**4 (6%)**	**4 (6%)**
DCFC	-	1 (1%)	1 (1%)
DM	-	1 (1%)	1 (1%)
HT + CVA + dyslipidemia + DM	-	1 (1%)	1 (1%)
HT + dyslipidemia	-	1 (1%)	1 (1%)
Total	**8 (12%)**	**61 (88%)**	69 (100%)

The profile of antiplatelet, comorbid conditions, and ischemic events seen in Table IV. Hypertension, Diabetes Melllitus, and Dyslipidemia is the most common comorbid conditions in patients with ischemic events.

High blood pressure is a major risk factor for coronary heart disease. A higher systolic pressure increases myocardial oxygen demand and the development of coronary atherosclerosis. This process results in angina pectoris (Weber T, Lang I, Zweiker R, *et al* 2016). Framingham's research also found a relationship between CHD and diastolic blood pressure. The incidence of myocardial infarction is 2x greater in the blood pressure group at 90-104 mmHg compared to 85 mmHg diastolic blood pressure, whereas in s ystolic blood pressure 105 mmHg 4x is greater (Nelwan EJ, Widjajanto E, Andarini S, *et al*¸ 2016). In Diabetes Mellitus patient, high blood glucose level can increase blood viscosity that can increase blood pressure and also can damage endothelium of blood vessel which can lead to atherosclerosis (Reiner et al, 2011). Dyslipidaemia also took place in ischemic events. It can be worsen coronary heart disease by increased plaque formation in the blood vessel.

Table V. Results of the *Naranjo scale* Algorithm score for adverse drug reactions

Patient	Therapy	Type of Bleeding	*Naranjo Scale Score*	Information
1	aspirin 80 mg aspirin 80 mg	Dyspepsia Bruised	3	Possible ADR
2	Aspirin 80 mg + clopidogrel 75 mg	Gums bleeding	4	Possible ADR
3	Aspirin 80 mg	Gastric Bruises	3	Possible ADR
4	Aspirin 80 mg	Gastric disturbance	3	Possible ADR

Incidence of *bleeding* in the use of antiplatelet is one of the side effects that occur. Bleeding that occurs can be known by signs such as bleeding in the gums, nasal bleeding, and the occurrence of bruises. In addition, antiplatelet therapy also causes gastrointestinal bleeding especially in elderly patients (Yasuda H, 2015). From 69 patients, side effects only occurred in 4 patients. Of

these 4 patients, 3 of them caused gastrointestinal disorders and 1 patient had gums bleeding.

After calculating the score using the *naranjo scale* on the occurrence of side effects on these 4 patients, it was found that 3 patients who had gastrointestinal disorders received a score of 3 and 1 patient who had bleeding gums got a score of 4 which is possible adverse drug reaction (ADR). To reduce the likelihood of ADR occurrence in the 4 patients above, the actions taken were that patient received PPI therapy and switched aspirin 80 mg to 75 mg clopidogrel, patient 2 who was using a combination of antiplatelet during the bleeding period changed to a single antiplatelet , patient 3 and 4 switch aspirin 80 mg with clopidogrel 75 mg.

IV. CONCLUSION

Ischemic events are higher in patients using Aspirin 80 mg with comorbid conditions: hypertension, dyslipidemia, and Diabetes Mellitus. The rate of adverse drug reaction is quite small, mostly occurs in Aspirin patients.

REFERENCES

Badan Penelitian dan Pengembangan Kesehatan Kementrian Kesehatan RI, 2018, *Riset Kesehatan Dasar,* Kementrian Kesehatan RI

Departemen Kesehatan RI, 2017, *Penyakit Jantung Penyebab Kematian Tertinggi, Kemenkes Ingatkan Cerdik,* Kementrian Kesehatan Republik Indonesia,1-2

Gregg D, J Pascal, Clermont G, 2003, *Platelets and Cardiovascular Disease.* American Heart Assoiciation Inc. 1-2

Hankey GJ, Eikelboom W, 2003, *Antiplatelet Drugs.* The Medical Journal of Australia. 178(11): 568

Hwang IC, Jeon JY, Kim Y, Kim HM,*et al,* 2015, *Association between Aspirin Therapy and Clinical Outcomes in Patienys with Non-Obstructive Coronary Artery Disease:A Cohort Study.*Plos One. 1-15

Ibanez B, James S, Agewall S, *et al,* 2017, *ESC Guidelines for the management of acute myocardial infraction in patients presenting with ST-segment elevation.* European Heart Journal. 30.

Ittaman SV., VanWormer JJ., Rezkalla SH., 2014. *The Role of Aspirin in the Prevention of Cardiovascular Disease*.Clin Med Res. 12(3-4): 147-154

Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. European Heart Journal (2019)00, 1-71

Listiyana AD, Mardiana, Prameswari GN, 2013, *Obesitas Sentral dan Kadar Kolesterol Darah Total.* Jurnal Kesehatan Masyrakat. 9(1): 38-39

Nelwan EJ, Widjajanto E, Andarini S, *et al*¸2016, *Modified Risk Factors for Coronary Heart Disease (CHD) in Minahasa Ethnic Group From Manado City Indonesia.* J.Exp.Life. 6(2): 91

Nicholaos Kakouros, Jeffrey J. Rade,Antonios Kourliouros, and Jon R. Resar, Platelet Function in Patients with DiabetesMellitus: From a Theoretical to a Practical Perspective. International Journal of Endocrinology.Volume 2011:1-14. doi:10.1155/2011/742719

Montalescot G, Sechtem U, Achenbach S, *et al*, 2013, *Guidelines On The Management of Stable Coronary Artery Disease*. European Heart Journal. 34 (38): 2949–3003

Pilgrim T, Windecker S, 2014, *Antiplatelet therapy for secondary prevention of coronary artery disease.* Heart. 100 (22): 1,3

Rodriguez G, Perez M, Hennekens CH, *et al*¸2016, *Bleeding Risk with Long-Term Low-Dose Aspirin: A Systematic Review of Observational Studies*. Plos One. 11(8): 9,14

Roffi M., Patrono C., Collet J., 2015, *Guidelines For The Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation.*European Heart Journal. 286

Tayeb HM, Nelson AJ, Willoughby SR, 2011, *Antiplatelet therapy in acute coronary syndromes: current agents and impact on patient outcomes*. Patient Relat Outcome Meas. 2: 7-19

Vanhees L, Rauch B, Piepoli M, *et al*, 2012. *Importance of Characteristic and Modalities of Physical Activity and Exercise in the Management of Cardiovascular Health in Individuals with Cardiovascular Disease (Part III).*European Journal of Preventive Cardiology. 19(6):1333-56.

WHO, 2011, *Global Atlas on Cardiovascular disease prevention and control*. Geneva: WHO

Yasuda H., Matsuo Y., Sato Y., *et a*l, 2015, *Treatment and Prevention of Gastrointestinal Bleeding in Patients Receiving Antiplatelet Therapy*, World Journal of Critical Care Medicine, 4 (1): 40-46, (online), (diakses 04-01-2018) https://www.wjgnet.com/2220-3141/full/v4/i1/40.htm

Weber T, Lang I, Zweiker R, *et al* 2016, *Hypertension and Coronary Artery Disease: epidemiology, physiology, effects of treatment and recommendations.*Wien Klin Wochenschr. 128(13-14):467