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*Original Research Article*

# The Pattern of Aspirin Use in Patients with Heart Failure at Mohammad Hoesin Hospital Palembang from 1st June 2013-30th July 2014

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## ABSTRACT

**Objective:** The aim of this study was to determine the prevalence of aspirin use in patients with HF.
**Method:** A drug utilization study has been done for 2 months through using medical records of patients with HF at Mohammad Hoesin Hospital from 1 June 2013-30 July 2014. There were 341 patients with HF who fulfilled inclusion criteria. Frequency descriptive used SPSS v.22.
**Results**: The highest proportion of patients with HF was in men (54.5%), aged 41-60 years (48.7%), and housewife (19.6%), prehypertension systolic (32.3%) and diastolic (34.3%) pressure, normal pulse rate (81.2%), and normal respiratory rate (53.7%). The prevalence of HF was 1.01%. The prevalence of aspirin use was 72.4% with the highest prevalence in men (44.28%), aged 41-60 years (36.95%), and history of Hypertensive Heart Disease (46.04%). The highest proportion of aspirin use was at dose of 80 mg/day (81.8%), using once a day (99.6%), and duration of ≤ 1 week (70.9%). 90.7% of aspirin were used with loop diuretics; mostly antagonist interactions (54.7%) were found in this study.
**Conclusions:** The prevalence of aspirin use in HF was moderate. The irregular use of single low-dose aspirin were widely used in patients with HF. There was high incidence of antagonistic interaction of aspirin in this study (54.7%).

***Key words:*** Aspirin, Heart failure, HF, Heart disease.

## INTRODUCTION

Heart failure (HF) is a clinical syndrome that occurs in patients who, because of an inherited or acquired abnormality of cardiac structure and/or function, develop a constellation of clinical symptoms (dyspnea and fatigue) and signs (edema and rales) that lead to frequent hospitalizations, a poor quality of life, and a shortened life expectancy. HF is a burgeoning problem worldwide, with more than 20 million people affected. [1] HF is estimated to almost present in 5% of patients who were hospitalized. [2]

HF is associated with a hypercoagulable state, formation of left ventricular thrombus, and cerebral embolism. It is also associated with both sudden death and death resulting from progressive HF that may be caused by unrecognized atherothrombotic events. As a result, there is a rationale for using antiplatelets to treat patients with HF. [3]

One of antiplatelet drugs is aspirin which is the result of acetylation of phenol

group. Aspirin can inhibit the synthesis of Thromboxane A2 which plays a role in platelet aggregation when used in low dose. Aspirin has been widely used as prevention of cardiovascular disease. Approximately 40 000 tons of aspirin are produced every year worldwide, and in the United States alone, 50 million people take 10 to 20 billion aspirin tablets regularly for the prevention of cardiovascular disease. [4]

The standard dosage of aspirin have increased the incidence of gastrointestinal bleeding compared to low dose and reported no benefit in the prevention of thrombotic events. [5] After reviewing the benefits and risks of aspirin, thrombus formation and bleeding respectively, a study was conducted to determine its utilization in patients with HF in order to provide more accurate information regarding its pattern today.

## MATERIALS AND METHODS

The study was carried out in the Internal Medicine ward of Mohammad Hoesin Hospital through using medical records from 1 June 2013-30 July 2014. The study populations were patients whose medical records were available in the internal medicine ward. The samples were all medical records of heart failure patients. The protocol has been approved by the ethics committee.

Inclusion criteria were medical records of patients with heart failure, which had complete data such as age, sex, occupation, blood pressure, and administration of drug. Patient's age limit was ≥18 years. Heart failure patients with comorbid disease (history of bleeding) were excluded in this study. All data will be described using SPSS v.22.

## RESULTS

Based on tracking of medical records during that period, there were 341 heart failure patients who met the inclusion and exclusion criterias as subjects of study. The majority of patients with heart failure in Mohammad Hoesin hospital (Table 1) were male (54.5%). The mean age of patients with heart failure in this study was 57.6 ± 13.5 years with the age group of 41-60 years (48.7%) had the most cases of heart failure among other age groups. Age group of >60 years had the second most cases of heart failure (39%) and the rest, age group of 18-40 years was 12.3%. Based on occupation, there were 40.8% patients had an unknown status of occupation and 1.2% of patients were *unemployed*. About 19.6% of patients with heart failure were housewives, making up the majority. College students, mechanics, carpenters, and family gatherings reported the lowest numbers (0.3%). The prevalence of heart failure in this study was 1.01% or 341/33681.

**TABLE 1: Characteristics of Patients with Heart Failure.**

| Characteristics | Total (n=341) | Percentage (n=100%) |
|---|---|---|
| **Sex** | | |
| Male | 186 | 54.5 |
| Female | 155 | 45.5 |
| **Age (year)** | | |
| 18-40 | 42 | 12.3 |
| 41-60 | 166 | 48.7 |
| >60 | 133 | 39.0 |
| **Occupation** | | |
| Unknown | 139 | 40.8 |
| Labor | 27 | 7.9 |
| Housewife | 67 | 19.6 |
| College Student | 1 | 0.3 |
| Mechanic | 1 | 0.3 |
| Merchant | 6 | 1.7 |
| Pensionary | 19 | 5.6 |
| Farmer | 15 | 4.4 |
| Official Government | 33 | 9.7 |
| Private Sector | 27 | 7.9 |
| *Unemployment* | 4 | 1.2 |
| Carpenter | 1 | 0.3 |
| Family Gathering | 1 | 0.3 |

In the group of systolic blood pressure (Table 2), patients with heart failure are most common in the prehypertension stage (32.3%). Only 26.7% had normal systolic blood pressure. About 3.5% had blood pressure ≥180 mmHg. The mean systolic blood pressure of patients with heart failure was 130.912 ± 23.4073 mmHg. Based on the diastolic pressure, heart failure patients who were in prehypertension stage became the highest group (34.3%) than other groups. Patients with heart failure who were in hypotension stage became the lowest group (2.1%). About 3.5% were in hypertensive

emergency and only 27.3% who had normal diastolic blood pressure. The mean diastolic blood pressure in patients with heart failure is 82.026 ± 13.5150 mmHg.

**TABLE 2: Distribution of Patients with Heart Failure.**

| Distribution | Total (n=341) | Percentage (n=100%) |
|---|---|---|
| **Systolic (mmHg)** | | |
| Normal (90-119) | 91 | 26.7 |
| Prehypertension (120-139) | 110 | 32.3 |
| Hypertension 1 (140–159) | 88 | 25.8 |
| Hypertension 2 (160–179) | 40 | 11.7 |
| Hypertensive emergency(≥180) | 12 | 3.5 |
| **Diastolic *(mmHg)*** | | |
| Hypotension (<60) | 7 | 2.1 |
| Normal (60-79) | 93 | 27.3 |
| Prehypertension (80-89) | 117 | 34.3 |
| Hypertension 1 (90–99) | 70 | 20.5 |
| Hypertension 2 (100–109) | 42 | 12.3 |
| Hypertensive emergency(≥110) | 12 | 3.5 |
| **Pulse Rate (x/min)** | | |
| Normal (60-100) | 277 | 81.2 |
| *Tachycardia* (>100) | 64 | 18.8 |
| Respiratory Rate (x/min) | | |
| Normal (16-24) | 183 | 53.7 |
| *Tachypnea* (>24) | 158 | 46.3 |

Mean pulse rate of patients with heart failure was 91.205 ± 15.6978 x/minute. The group of patients who had normal pulse rate (60-100 x/min) was the highest group (81.2%) in patients with heart failure (Table 2) and the rest, about 18.8% had rapid pulse rate. Based on respiratory rate, heart failure patients with normal respiratory rate (16-24 x/min) had higher number than other groups (53.7%). About 46.3% of patients had increased breathing effort. Mean respiratory rate of patients with heart failure was 25.683 ± 5.0642 x/minute.

**TABLE 3: Prevalence of Aspirin Use.**

| Prevalence | Aspirin (+) (n=247) | Aspirin (-) (n=94) |
|---|---|---|
| **Sex** | | |
| Male | 151 (44.3%) | 35 (10.3%) |
| Female | 96 (28.2%) | 59 (17.3%) |
| **Age (year)** | | |
| 18-40 | 23 (6.7%) | 19 (5.6%) |
| 41-60 | 126 (37%) | 40 (11.7%) |
| >60 | 98 (28.7%) | 35 (10.3%) |
| **History** | | |
| Coronary Heart Disease | 93 (27.3%) | 27 (7.9%) |
| Angina Pectoris | 5 (1.5%) | 2 (0.6%) |
| Atrial Fibrillation | 31 (9.1%) | 15 (4.4%) |
| Stroke | 3 (0.9%) | 1 (0.3%) |
| Congenital Heart Disease | 2 (0.6%) | 1 (0.3%) |
| Heart Valve Disease | 23 (6.7%) | 8 (2.3%) |
| Cardiomyopathy | 18 (5.3%) | 11 (3.2%) |
| Diabetes Mellitus | 34 (10%) | 14 (4.1%) |
| Thyroid Heart Disease | 2 (0.6%) | 2 (0.6%) |
| Hypertensive Heart Disease | 157 (46%) | 49 (14.4%) |

247 out of 341 patients (72.4%) with heart failure received aspirin during treatment. The aspirin use in patients with heart failure (Table 3) was more common in male patients (44.3% or 151/341). In female patients, the prevalence of aspirin use was 28.2% (96/341). At age group of 18-40 years, the prevalence of its use was 6.7% or 23/341. The aspirin use in heart failure at age group of 41-60 years had the highest prevalence (Table 3) about 37% or 126/341, while in the age group of >60 years, the prevalence of aspirin use was 28.7% or 98/341. The mean age of aspirin users in this study was 58.31 ± 12.491 years.

Patients with history of Hypertensive Heart Disease were the largest group using aspirin (Table 3) which its prevalence of use was 46%. The lowest prevalence of aspirin use was found in patients with history of Thyroid Heart Disease (0.6%) and Congenital Heart Disease (0.6%). History of coronary heart disease which is usually the main indication of aspirin use was the second largest group with prevalence of 27.3%. The other prevalence of aspirin users based on history of disease are as follows, angina pectoris by 1.5%, Atrial Fibrillation by 9.1%, Stroke by 0.9%, Heart Valve Disease by 6.7%, Cardiomyopathy by 5.3%, and Diabetes Mellitus by 10.0%.

**TABLE 4: Aspirin Use in Patients with Heart Failure.**

| Aspirin | Total (n=247) | Percentage (n=100%) |
|---|---|---|
| **Dosage** | | |
| 80 mg/day | 202 | 81.8 |
| 100 mg/day | 43 | 17.4 |
| 160 mg/day | 1 | 0.4 |
| 200 mg/day | 1 | 0.4 |
| **Frequency** | | |
| 1 x/day | 246 | 99.6 |
| 2 x/day | 1 | 0.4 |
| **Duration** | | |
| > 1 week | 72 | 29.1 |
| ≤ 1 week | 175 | 70.9 |

Of 247 patients taking aspirin (Table 4), there were 81.8% using dose of 80 mg/day, 17.4% using dose of 100 mg/day, 0.4% using dose of 160 mg/day, and 0.4% using dose of 200 mg/day. The mean dose of aspirin used in this study was 84.291 ± 11.661 mg/day. The majority of patients with heart failure using aspirin were given

the frequency of once a day (99.6%). Frequency of use of twice a day was only given in 1 patient (0.4%). Most of aspirin use in patients with heart failure was at duration of ≤ 1 week (70.9%). The group receiving aspirin for >1 week was about 29.1%. The mean duration of aspirin use was 6.09 ± 4.066 days.

**TABLE 5: Drug Interactions with Aspirin.**

| Interact with Aspirin | Total | Percentage (%) |
|---|---|---|
| *Loop Diuretic* | 224 | 90.7 |
| *Aldosterone Antagonist* | 126 | 51.0 |
| Calcium Channel Blocker | 17 | 6.9 |
| ACE-Inhibitor | 128 | 51.8 |
| Angiotensin Receptor Blocker | 65 | 26.3 |
| *Beta blocker* | 23 | 9.3 |
| Digitalis | 79 | 32.0 |
| Other Antiplatelet | 48 | 19.4 |
| Anticoagulant | 25 | 10.1 |
| Vasodilator | 32 | 13.0 |
| Prostacyclin analogue | 4 | 1.6 |
| *Alpha Agonist* | 5 | 2 |
| Antiarrhythmic | 2 | 0.8 |
| Vasopressor | 2 | 0.8 |
| Proton Pump Inhibitor | 115 | 46.6 |

Loop diuretics was the most common drug (90.7%) used together with aspirin in patients with heart failure (Table 5). The combination of ACE-inhibitors and aspirin were the second highest (51.8%) combination used in patients with heart failure. The rest, aspirin was used with aldosterone antagonists/Spironolactone (51%), Calcium Channel Blockers (6.9%), Angiotensin Receptor Blocker (26.3%), beta blockers (9.3%), digitalis/digoxin (32.0%), other antiplatelet/clopidogrel (19.4%), anticoagulant/warfarin (10.1%), vasodilators/antianginal (13.0%), Proton Pump Inhibitors (46.6%), analog prostacyclin/Dorner® (1.6%), alpha agonist/clonidine (2%), antiarrhythmics (0.8%), and vasopressors/dopamine (0.8%).

**TABLE 6: Types of Pharmacodynamic Drug Interactions with Aspirin.**

| Types of Interactions | Total (n=895) | Percentage (n=100%) |
|---|---|---|
| *Additive* | 48 | 5.4 |
| Potentiation | 79 | 8.8 |
| *Synergistic* | 25 | 2.8 |
| *Antagonistic* | 490 | 54.7 |
| No Interaction | 253 | 28.3 |

In this study, the antagonist interaction (Table 6) was the most common interaction (54.7%). Other types of interactions in this study include additive (5.4%), potentiation (8.8%), synergistic (2.8%). About 253 combinations of drugs (28.3%) didn't have interaction. There were interaction of aspirin with aldosterone antagonist (spironolactone), ARB, Calcium Channel Blockers, vasodilators (Isosorbide dinitrate and isosorbide mononitrate), analog prostacyclin, alpha agonists, antiarrhythmics, and vasopressors (dopamine).

## DISCUSSION

Of 341 patients with heart failure, most of them were male (54.5%), aged 41-60 years (48.7%), and housewife (19.6%). These results were similar with study conducted by Pakpahan (2011) in Herna Medan Hospital who found that majority of heart failure patients were male (57.6%), age group of ≥40 years (96.5%), and Housewife (37.8%). [6] Similar results were also found in the HCU and ICU Dr. Kariadi Semarang hospital by Kumalasari (2013) who showed most of heart failure patients were men (56.8%) and aged 41-60 years (40.9%). [7] Prevalence in this study (1.01%) was much higher than study by Riskedas (2013) who found the prevalence of heart failure in Indonesia based on interviews of diagnosed was 0.13% and based on diagnosed by doctor or symptoms was 0.3%. [8]

Based on blood pressure, prehypertension stage of blood pressure was most common in patients with heart failure, both systolic (32.3%) and diastolic (34.3%). Mean systolic pressure was 130.912 ± 23.4073 mmHg. The mean diastolic pressure was 82.026 ± 13.5150 mmHg. These results were different from results of study by Gheorghiade et al (2006) who conducted a study on systolic blood pressure when patients with heart failure admitted to hospital. Their study showed the highest group was the group with systolic blood pressure of <120 mmHg (25.2%). Patients with blood pressure of 120-139 mmHg are the group with the lowest number (24.9%). In their study, systolic blood pressure in

patients with heart failure on admission was independent prognostic information that is important. [9] Another study by Kitzman et al (2010) showed mean systolic blood pressure of heart failure patients was 147 ± 20 mmHg and other study by Edelmann et al (2011) showed mean systolic blood pressure of heart failure patients was 140 ± 19 mmHg. [10,11] The mean systolic blood pressure of their study was slightly higher compared to this study. Results of another study by Goernig et al (2014) showed mean systolic blood pressure and diastolic heart failure patients were lower than this study, namely 115 ± 22 mmHg and 54 ± 13 mmHg. [12]

The group of patients who had normal pulse rate was the most common group in heart failure patients (81.2%). Mean pulse rate was 91.205 ± 15.6978 x/min. Results of this study was different from study by Kitzman et al (2010) and Edelmann et al (2011) who found mean pulse rate in their study was more lower than this study. In Kitzman et al's study, mean pulse rate of patients with heart failure was 68 ± 13 x/min, while study by Edelmann et al showed mean pulse rate of patients with heart failure was 66 ± 11 x/min. [10,11]

Heart failure patients with normal respiratory rate were most common in this study (53.7%). Mean respiratory rate was 25.683 ± 5.0642 x/min. Results of this study were not much different from study by Bhatia et al (2006). In that study, Bhatia et al found that heart failure patients with ejection fraction <40% and >50% had mean respiratory rate was not much different in this study, about 26 x/min. [13]

In this study, the prevalence of aspirin use in patients with heart failure was moderate (72.4%). The result was consistent with the result of study conducted by Bermingham et al (2014) through a retrospective cohort study. In that study, most of patients with heart failure used aspirin (60.4%), but the prevalence of its use was lower than this study with patients prescribed aspirin for 100% follow-up were 77.8%. [14] Result by Chang et al (2010) also showed high prevalence of aspirin use in patients with heart failure (55.9%). [15] Different result of this study was conducted by Gheorghiade et al (2006) who showed that aspirin was only used by 39.53% of patients with heart failure. [9] A study by Abu-Gharbieh et al (2011) showed the prevalence of aspirin use in patients with congestive heart failure (CHF) was 96.6% in Jordan and 85.7% in the UAE. This prevalence is higher because samples of CHF patient samples used too little when compared with this study. [16]

Heart failure is associated with hypercoagulable state, left ventricular thrombus formation and cerebral embolism. [3] Platelet abnormalities in heart failure patients have been well described in many studies. For example, heart failure patients have increased whole blood aggregation and higher mean platelet volume and soluble (and platelet-bound) P-selectin. [17] Increased platelet activity is the reason for antiplatelet use especially aspirin in patients with heart failure to prevent thrombus formation.

Effective and safe aspirin use for the prevention of cardiovascular disease has been denied by Cleland (2002) who made three main points why aspirin is doubtful benefits. First, Antiplatelet activity of aspirin is not as safe and effective as widely believed. Second, all large, long term trials involving people treated with aspirin after having a heart attack shows no benefit for mortality. In other words, those who take aspirin don't live any longer than those who don't. Third, aspirin seems to change the way vascular events present themselves, rather than preventing them. The number of nonfatal events may be reduced, but there is an increase in sudden deaths. Aspirin may conceal a cardiac event in progress. He stated that studies claiming aspirin is beneficial are seriously flawed, and interpretation of those studies is biased. [18] Through study about Warfarin/Aspirin Study in Heart failure, Cleland et al (2004) also showed that the efficacy and safety of

aspirin in patients with heart failure has no convincing evidence. [19] The prevalence of aspirin use in male patients (44.3%) was higher than women. The results are similar with study by Bermingham et al (2014) who found male heart failure patients (64.1%) taking more aspirin than women. [14] Study conducted by Chang et al (2010) also gave similar results. In their study, the proportion of aspirin use in patients with heart failure was higher in male (70.4%) than women. [15] Similar results were also found by Abu-Gharbieh et al (2011) in a study on prevalence of aspirin use, but using different samples, namely patients of cardiovascular disease (not only patients with heart failure). Study results showed that men are significantly more prescribed aspirin than women, both in Jordan (89 versus 82%; p=0.034) and UAE (79 versus 59%; p=0.001). [16]

Aspirin users were higher in men than women. This may be caused by various factors, such as benefits and effectiveness. Some of clinical Trials have indicated that aspirin may be more benefit to male patients than to female patients with clinical complications of atherosclerosis. [20] Another study found that doses of aspirin that inhibited thrombus formation in males were ineffective in females. [20] Sadeghi et al (2012) even showed that about 75.3% of aspirin resistance occurred more in women than men, so that aspirin use in women should be more aware. A probable reason for resistance may be due to polymorphism in COX-1 and COX-2 genes and other metabolites of arachidonic acid. [21] Their study results could be the reason why more men were given aspirin than women.

The highest prevalence of aspirin use was in age group of 41-60 years (37%). Mean age of aspirin users in this study was 58.31 ± 12.491 years. This study results were different from study conducted by Bermingham et al (2014). The mean age of aspirin users in their study (71.9 ± 11.2 years) were older than this study. [14] Different results were also shown by Chang et al (2010) who found mean age of aspirin users with heart failure of 66.1 ± 10.4 years. [15] Abu-Gharbieh et al (2011) also showed different results that most aspirin users was at age group of >60 years in Jordan and UAE. [16] The aspirin use to prevent thrombus formation is recommended in elderly. In old age, arteries will become stiff and dilated due to degeneration of elastic fibers, an increase in collagen and calcium content, and by a decrease in prostacyclin and nitric oxide with related reduction in endothelium-dependent dilation. There is also increased binding of platelet-derived growth factor to arteries, caused by changes in the glycosaminoglycan content of the vessel wall, which enhances the progression of atherosclerosis and indirectly contributes to atherothrombosis. [22] Atherothrombotic events can be prevented by aspirin through inhibition of COX-1 that synthesizes TXA2 in order to reduce the risk of thrombus formation. [23]Therefore, aspirin may be beneficial in the elderly because of the high risk of atherothrombosis incident, but the safety of its use in the elderly is still questionable and concern in the world.

Heart failure patients with history of Hypertensive Heart Disease (HHD) were the highest prevalence of aspirin users in this study (46.0%). These results were different from results found by Bermingham et al (2014) who showed that most of aspirin users had comorbid Any Ischaemic Heart Disease by 56.8%. In their study, an aspirin user with comorbid hypertension was 45.2%. [14] The study by Chang et al (2010) also showed different results. Most of aspirin users with heart failure had history of Ischaemic Heart Disease (75.2%). Heart failure patients with history of hypertension who used aspirin were the lowest group (10.5%). [15]

Aspirin is usually recommended in patients with heart failure post myocardial infarction to prevent recurrence of myocardial infarction. It is due to the presence of intimal injury in heart failure through increased von Willebrand factor which plays a role in reinfarction. [24] But its use in patients with history of HHD may be

beneficial. Based on study by Zanchetti et al (2002), low-dose aspirin (75 mg/day) were considered to be benefit and should be recommended as a treatment in well-treated hypertensive patients at risk for cardiovascular disease because it has shown a significantly reduction of cardiovascular events and myocardial infarction. [25]

Aspirin dose of 80 mg/day are the most widely used (81.8%). The mean dosage was 84.291 ± 11.661 mg/day. This study results were not much different from results of Bermingham et al (2014) who showed that mean dose of aspirin use are at low dose (89 ±52mg) with 92.8% of patients were given aspirin at dose of 75 mg/day. [14]

Low-dose aspirin in this study was different from Bermingham et al. Low dose in this study was 80 mg while low doses in Bermingham et al study was 75 mg. Differences were probably due to the available preparation in Mohammad Hoesin hospital was dosage of 80 mg. Although there are differences in the dose, most of dose aspirin used in both study has followed the guidelines recommended by American Heart Association that aspirin used at daily dose of 75-160 mg when used for primary prevention of cardiovascular disease. [26]

Although dose of aspirin used was low, but its effectiveness was equally or even more beneficial than the standard dosage. The standard dosage (325 mg) is associated with a significantly higher risk of gastrointestinal bleeding (including fatal bleeds) than in low dose. And here is the irony: studies have shown that standard doses of aspirin offer no advantage in preventing thrombotic events compared with lower doses. [5]

Targets of aspirin are COX-1 and COX-2. There is 60% homology between the amino acid structures of COX-1 and COX-2 and aspirin binds to Ser 516 in the active site of COX-2 in the same way as it binds to Ser 530 in the active site of COX-1. However, the active site of COX-2 is slightly larger than the active site of COX-1, so that arachidonic acid can still 'squeeze past' the aspirin molecule inactivating COX-2 and become converted to 15-R-HETE. [27] Inhibition of COX-1 which plays a role in platelet function can be achieved with low-dose aspirin once a day, while the inhibition of COX-2 as an anti-inflammatory required higher doses. [4]

Aspirin affects a balance between TXA2, which is released from platelets, and prostacyclin, which is made by the blood vessel walls. Prostacyclin is a gastric mucosal protective agent that is often associated with the incidence of gastric bleeding due to its reduced when used with drugs known as NSAIDs. Despite the anti-cyclooxygenase activity of aspirin, prostacyclin is produced continuously in endothelial cells because they recover the ability to synthesise cyclooxygenase within a few hours. However, platelets cannot make fresh cyclooxygenase; consequently, TXA2 synthesis only resumes when new platelets are made (The life of a platelet lasts for 8 to 11 days). Thus, treatment with low-dose aspirin (75-100 mg/dL) will lead to a cumulative inhibition of TXA2 formation in platelets, while the production of prostacyclin will continue. [28]

Salicylate bond with albumin depending on its concentration. At clinical concentrations, from 50-90% of the salicylate is bound to albumin, while acetylsalicylic acid itself is bound to only a very limited extent. [23] The lower the concentration in the plasma, the higher the bonding with albumin. Its bond with albumin can affect the distribution in the body, both local and systemic. Therefore, the amount of dosage use should be considered.

Plasma half-life of aspirin about 13-19 minutes but the inhibitory effect of platelet aggregation factor lasts for the life of platelet (5-10 days). Therefore, duration action of aspirin is usually less dependent on the half-life so that the aspirin use is recommended once a day. [23] In this study, the frequency of aspirin use of 1x/day (99.6%) can be said to be appropriate because using once a day has been able to provide promotive effect to prevent of

thromboembolism in patients with heart failure. Excessive aspirin use likely caused other effects such as bleeding, particularly in gastrointestinal. [5]

Frequency of aspirin use of once a day is usually used as an antiplatelet therapy for prevention of cardiovascular disease, while the frequency of use of 4-6 times/day is usually used as an *anti-inflammatory*. [23] Its use as an analgesic requires higher doses than as antiplatelet so analgesic dose should be divided. The use of divided high-dose was intended to inhibit COX-2 potently than COX-1. This was due to COX-2 was largely found in inflammatory cells and could be induced with mitogens, growth factors, tumor promoters, and lipopolysaccharides and in turn produced prostaglandin E2 during pathophysiological processes such as hyperalgesia and inflammatory reactions. [4] As an antiplatelet, it only is used once a day because only low dose needed to inhibit COX-1 which was found in platelets.

Administration of aspirin in prevention of thrombus should be done routinely. In this study, most patients with heart failure consumed aspirin for ≤1 week (70.9%), which the administration of Aspirin should be done regularly or daily in patients at risk of ischemic events. Routine use can provide benefit to inhibit new platelets that are constantly being released into the circulation. [26]

Long-term of aspirin use confers conclusive net benefits on risk of subsequent myocardial infarction, stroke, and vascular death among patients with a wide range of prior manifestations of cardiovascular disease. [29] Data showed that the aspirin use for patients treated for 2 years had reduced the risk of cardiovascular events by approximately 22%. [26] Although it was recommended to be used routinely, regular use of aspirin has been reported to increase the incidence of gastrointestinal bleeding, [30] duodenal ulcers, kidney failure, and salicylate toxicity.

Platelets which were inhibited by aspirin cannot generate new COX, the effects of aspirin irreversibly last for the duration of the life of the platelet (≈10 days). After a single dose of aspirin, COX activity recovers by ≈10% per day as a function of platelet turnover. As a result, platelets may take 10 days to be able to restore normal COX activity so duration of use must be considered. However if as little as 20% of platelets have normal COX activity, hemostasis may be normal. [31]

Loop diuretics were the most widely drug (90.7%) that used together with aspirin. *These results were consistent with* study of Bermingham et al (2014) which showed loop diuretics were the most widely drug (85.5%) that used together with aspirin. [14] Same results by Chang et al (2010) also showed that aspirin was widely used together with diuretics (78.2%) in patients with heart failure. [15]

In this study, aspirin was widely used together with loop diuretics. This is due to drug of choice for a patient with heart failure is a diuretic which treats fluid overload as a result of ventricular pump dysfunction of the heart. However, the combination of these drugs can be harmful because many researchers theorize that salicylates can inhibit the effects of loop diuretics on renal mediated by prostaglandins, including an increase in sodium excretion, renal blood flow, and plasma renin activity. [23]

The interaction of these drugs were studied by Wilson et al (1986) and they concluded that chronic low-dose aspirin can profoundly affect platelet prostaglandin production without affecting stimulated renal PGI2 production or plasma renin activity. The study showed that patient who underwent one week of treatment did not show any change in weight, blood pressure, or diuretic and natriuretic responses to furosemide with aspirin. [32] Another study by Jhund et al (2001) showed aspirin inhibits acute venodilator effect of furosemide in patients with chronic heart failure. [33] Combination of aspirin along with furosemide should be wary considering loop diuretic is drug of choice in patients with heart failure.

A total of 128 ACE-I which was used with aspirin may be aware because aspirin can reduce the effects of ACE-I in patients with heart failure. Ahmed (2000) conducted an investigation through data from clinical trials. Results showed there is a theoretical possibility that the negative interaction between ACE inhibitors and aspirin may reduce the beneficial effects of ACE inhibitors. [34] However Zanchetti et al (2002) found that long-term low-dose aspirin does not interfere with blood pressure-lowering effect of ACE-I. [35] Similar results which were shown by Aumégeat et al (2003) showed that there were no interaction between aspirin and ACE-I. [36] In contrast to ACE-I, a total of 65 combinations of aspirin with ARB didn't have interaction because study of Chang et al (2010) showed no significant modification of the benefit of ARBs (Candesartan) by concomitant use of aspirin in patients with Heart Failure. [15]

The combination of aspirin with other antiplatelet can be accessed through study by Serebruany et al (2003) who proved treatment of aspirin along with clopidogrel for 1 month provides significantly greater inhibition of platelet activity than aspirin alone in patients with CHF. In their study, the use of aspirin and clopidogrel may decrease mortality rates by reducing the incidence of thrombotic events in patients with heightened platelet activity. [37]

Based on pharmacodynamics, drug interactions are classified into synergistic, antagonistic, additive, and potentiation. An interaction among antiplatelet (5.4%), aspirin and clopidogrel is an additive interaction that arise through the same action of inhibiting aggregation platelet. [23] Aspirin's target is COX-1 whereas clopidogrel's target is $P2Y_{12}$. Both of these targets are present in platelets. Synergistic interaction between aspirin and warfarin was rarely found (2.8%). Besides they have same action in preventing thrombus formation, aspirin can displace warfarin from protein binding sites, leading to increase of warfarin's action. [23,38] These interactions can be dangerous because it can cause fatal bleeding.

Potentiation interaction that found was interaction between aspirin and digoxin (8.8%). These interactions can lead to an increase in plasma concentration of digoxin due to decrease in renal excretion by aspirin. This can cause toxic effect. [23] Antagonistic interactions were the most common interactions (54.7%) found in this study. there were interaction between aspirin with loop diuretics, ACE-I, beta blockers, and Proton Pump Inhibitors (PPIs). Aspirin can decrease glomerular filtration via decreased prostaglandin synthesis. [23] As a result, sodium excretion may be decreased, thereby reducing the effects of loop diuretics. This combination may also increase the risk of acute renal failure and salicylate toxicity because its excretion via glomerulus filtration. [38]

The hyponatremic and hypotensive effects of ACE inhibitors may be diminished by the concomitant administration of aspirin due to its indirect effect on the renin-angiotensin conversion pathway, leading to decreased glomerulus filtration. [23] Its action was also known to inhibit breakdown of the potent vasodilator bradykinin, which stimulates prostaglandin synthesis. Aspirin's action can reduce the vasodilator effects of ACE-I through inhibit COX-1 irreversibly, thereby reducing the production of vasodilator prostaglandins. [39] Efficacy of ACE-I appears to be slightly reduced by low-dose aspirin. [38]

Aspirin can reduce the hypotensive effects of beta blockers through inhibition of renal prostaglandins, leading to decreased renal blood flow, and salt and fluid retention. [23] PPIs may reduce platelet response to aspirin, as shown by increased residual platelet aggregation and platelet activation when they were used together. [40] This probably due to PPI may interfere with the absorption and bioavailability of aspirin by altering gastric acidity. [41]

## CONCLUSION

The prevalence of aspirin use in patients with heart failure was moderate (72.4%). Aspirin was widely used in male, aged 41-60 years, and having history of Hypertensive Heart Disease. Single low dose aspirin with duration of ≤1 week was the most commonly used in patients with heart failure. Aspirin was widely used along with loop diuretics and there was high incidence of antagonistic interactions of aspirin with other drugs.

### *Conflict of Interests*

The authors declare that there is no conflict of interests regarding the publication of this paper.


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