

Medication Persistence to Lipid-Lowering Agents as Cost-Saving Opportunities in Indonesian Patients with Acute Coronary Syndrome after Percutaneous Coronary Intervention

Erna Kristin¹, Lucia Krisdinarti², Alfi Yasmina³, Woro Rukmi Pratiwi¹, Ratih Puspita Febrinasari⁴, Endang Mahati⁵ and Sudi Indrajaya^{1*}

¹ Department of Pharmacology & Therapy, Faculty of Medicine Public Health and Nursing, Universitas Gadjah Mada, Sekip Utara 55281 Yogyakarta, Indonesia

² Department of Cardiology and Vascular Medicine, Faculty of Medicine Public Health and Nursing, Universitas Gadjah Mada, Sekip Utara 55281 Yogyakarta, Indonesia

³ Department of Pharmacology, Faculty of Medicine, Universitas Lambung Mangkurat, 70123 Banjarmasin, Indonesia

⁴ Department of Pharmacology, Faculty of Medicine, Universitas Sebelas Maret, 57126 Surakarta, Indonesia

⁵ Department of Pharmacology, Faculty of Medicine, Universitas Diponegoro, 50275 Semarang, Indonesia

ABSTRACT

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*Corresponding author
Sudi Indra Jaya

Email:
indrajaya.sudi@ugm.ac.id

Medication persistence is known to reduce acute coronary syndrome (ACS) disease mortality. As much as 13% of Indonesia's budget for national health insurance programs was used for cardiovascular disease. The number of population-based studies discussing the cost-saving opportunities of medication persistence in ACS patients undergoing percutaneous coronary intervention (PCI) is still minimal. This study aimed to investigate the estimated cost saving of persistence to lipid-lowering agents in patients with ACS after their first PCI. This hospital-based, retrospective cohort study with 2-years follow-up was conducted with 367 patients. Patients were considered having medication persistence if the gap between prescriptions was ≤ 30 days. Persistence assessment was done for lipid-modifying agents (WHO ATC Code: C10). The main outcome is cost-saving opportunities assessed by dividing the difference in total costs resulting from medication persistence with the difference in the proportion of major adverse cardiovascular events (MACE) and major adverse cardiovascular and cerebrovascular events (MACCE) prevented by medication persistence. The study found that direct medical costs incurred by persistent patients were significantly lower than non-persistent patients with lipid-lowering agents (IDR 9,535,209.76 versus IDR 15,933,959.28). Persistence to lipid-lowering therapy can prevent one MACE incident with cost-saving of IDR 996,192.41 when compared to non-persistence patients, while one MACCE incident can be prevented with cost-saving of IDR 733,103.02. Our study indicates that among ACS patients who underwent their first PCI, medication persistence with lipid-lowering agents can contribute to cost-saving in preventing one MACE or MACCE event.

Keywords: cost saving, persistence to treatment, acute coronary syndrome, percutaneous coronary intervention

INTRODUCTION

According to the Indonesia Basic Health Research (*Riskesmas*), the prevalence of cardiovascular disease (CVD) rose to 1.5% in 2018, increasing with age (Ministry of Health of Indonesia, 2018). The high prevalence of CVD has a major socio-economic impact because drug therapy for CVD is required continuously, and the treatment is expensive. Also, there is a need for additional diagnostic or therapeutic tools, the presence of comorbidities, the long duration of treatment, and the high costs that affect the budget of the Indonesian national health insurance. In 2019, the Indonesian Healthcare and Social Security Agency (*Badan Penyelenggara Jaminan Sosial Kesehatan*) reported that financing for CVD accounted for almost 13% of the national health insurance spending and become the number one high-cost catastrophic disease (BPJS Kesehatan, 2020).

In this study, we focused on patients with Acute Coronary Syndrome (ACS) undergoing their first Percutaneous Coronary Intervention (PCI). PCI is recommended for patients with ACS, which is a life-threatening condition that carries a high risk of recurrent cardiovascular events and death. Previous studies have shown that PCI can promote recovery in patients with ACS (Amsterdam *et al.*, 2014; Anderson, 2013; Perhimpunan Dokter Spesialis Kardiovaskular Indonesia (PERKI), 2018). This condition may become worse in the presence of comorbid conditions such as diabetes mellitus, hypertension, dyslipidemia, and obesity (Fassa *et al.*, 2010). A long-term pharmacological approach is very important for secondary prevention in patients with ACS, and one of them is lipid management (Claessen *et al.*, 2020). The European Society of Cardiology recommends lipid-lowering therapy in all ACS patients without any contraindication or definite history of intolerance (Mach *et al.*, 2020). These data will be useful for policymakers in reviewing ACS management to help in budget allocation and to encourage patient compliance during the treatment period. This study aimed to investigate the estimated cost saving of persistence to treatment with lipid lowering agents in patients with ACS undergoing PCI, adjusted for various patient characteristics at baseline.

MATERIALS AND METHODS

We used medical records and administrative medical claims data from five hospitals in Indonesia with catheterization laboratory facilities. The subjects of this study were patients with ACS who underwent their first PCI. Data were collected from

January 2019 to February 2020. Trained enumerators conducted the data collection. Institutional protocol approval was obtained from the Medical and Health Research Ethics Committee (MHREC), Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada. Inclusion criteria for the study were as follows: (1) 18 years of age or older; and (2) patients having PCI procedure for the first time. The exclusion criteria for the study were as follows: (1) Medical record data were incomplete or unavailable; (2) Patients with pregnancy; (3) Patients diagnosed with chronic kidney disease; and (4) Patients diagnosed with cancer.

Patients were defined as having the persistence to treatment if the gap between prescriptions was ≤ 30 days. We assessed persistence with lipid-modifying agents (WHO ATC Code C10). The main outcome was cost-saving opportunities assessed by dividing the difference in total costs resulting from persistence to treatment with the difference in the proportion of major adverse cardiac event (MACE) and major adverse cardiovascular and cerebrovascular events (MACCE) prevented by persistence to treatment. MACE is defined as a composite of repeat PCI, myocardial infarction, or all-cause death. Meanwhile, MACCE is defined as a composite of repeat PCI, myocardial infarction, stroke, or all-cause death. The costs of medication assessed were inpatient and outpatient costs consisting of administration costs, drugs, consumable materials, medical procedures by a doctor, medical procedures by other medical professions, laboratory tests, other supporting examinations, accommodations, doctors' consultation services, use of medical devices, and other consulting services.

Baseline characteristics of patients with ACS undergoing PCI were analyzed descriptively. Categorical data are presented in frequency and proportion, while continuous data are expressed as mean \pm standard deviation (SD). Persistence to treatment was presented with the Kaplan-Meier method, and stratified by gender, age, history of hypertension, history of diabetes mellitus, and history of cardiovascular diseases followed by a log-rank test to see if there were any significant differences. The relationship between persistence to treatment and treatment costs was analyzed by the Mann-Whitney test because the data were not normally distributed. The 95% confidence level was used with $p < 0.05$ set as significant. Statistical analysis was performed with Excel (Microsoft Corp., Washington, U.S.) and SPSS Statistics Version 23 (IBM Corp., Armonk, NY).

Table I. Baseline characteristics.

Characteristics	Total (n = 367) n (%)	Lipid-lowering agents	
		P (n = 286, 77.9%) n (%)	NP (n = 81, 22.1%) n (%)
Gender			
Males	312 (85.0)	241 (84.3)	71 (87.7)
Females	55 (15.0)	45 (15.7)	10 (12.3)
Age (years), Mean (\pm SD)	58.8 (9.7)	59.0 (10.0)	58.3 (8.8)
Education level			
High school or below	229 (62.4)	181 (63.0)	48 (60.0)
Higher than high school	82 (22.3)	105 (37.0)	33 (40.0)
Comorbidities			
Diabetes mellitus	88 (24.0)	64 (22.4)	24 (29.6)
Hypertension	134 (36.5)	103 (36.0)	31 (38.3)
Cardiovascular diseases	106 (28.9)	82 (28.7)	24 (29.6)
Cerebrovascular diseases	5 (1.4)	3 (1.0)	2 (2.5)
Respiratory diseases	16 (4.4)	9 (3.1)	7 (8.6)
Gastrointestinal diseases	21 (5.7)	12 (4.2)	9 (11.1)
Body mass index (kg/m ²), Mean (\pm SD)	24.7 (4.0)	24.7 (4.0)	24.5 (3.9)
Lipid Profile			
Total Cholesterol, Mean (\pm SD)	185.7 (45.0)	184.0 (42.6)	191.7 (52.6)
LDL-cholesterol, Mean (\pm SD)	125.0 (36.3)	125.2 (33.9)	124.5 (44.2)
HDL-cholesterol, Mean (\pm SD)	43.2 (16.3)	43.4 (17.1)	42.8 (13.4)
Triglycerides, Mean (\pm SD)	141.6 (70.5)	137.9 (66.1)	154.4 (83.5)
Hospital admission			
Emergency Unit	288 (78.5)	231 (80.8)	57 (70.4)
Outpatient Clinic	78 (21.3)	54 (18.9)	24 (29.6)
No data	1 (0.3)	1 (0.3)	0 (0.0)
Payment method			
National health insurance (JKN)	330 (89.9)	253 (88.5)	77 (95.1)
Other payment methods	36 (9.8)	33 (11.2)	4 (4.9)
No data	1 (0.3)	1 (0.3)	0 (0.0)

Note: P = persistence, NP = non-persistence, SD = standard deviation, JKN = *Jaminan Kesehatan Nasional*.

RESULTS AND DISCUSSION

Characteristics of the subject

Patients with ACS who underwent PCI and met the inclusion and exclusion criteria in the study were 367 people. From those, 267 patients had complete medication cost data for cost analysis. Most of the patients were male (85.0%), with an average age of 58.8 \pm 9.7 years. Comorbidities (history of diabetes mellitus, hypertension, cardiovascular diseases, cerebrovascular disease, respiratory disease, and gastrointestinal disease) were found in 24.0-36.5% of patients. At baseline, the patients' mean body mass index (BMI) was in the normal category (24.7 \pm 4.0kg/m²). The average lipid profile at baseline was still in the normal category (Table I).

Based on the use of lipid-modifying agents, most patients showed persistence to treatment (77.9%). Patients who are non-persistent with lipid-lowering drugs tend to have a lower education level of high school or below, have a history of diabetes mellitus, have a higher total cholesterol level, higher triglyceride levels, and are less likely to use the Indonesian national health insurance (*Jaminan Kesehatan Nasional*/JKN).

Persistence to Treatment with Lipid-lowering Medication

The median follow-up duration for lipid-lowering therapy was 7.9 (IQR: 2.2-17.0) months. The Kaplan-Meier curve (Figure 1) shows that there was a rapid (24.5%) decline in cumulative

persistence of lipid-lowering medication in the first year, then the decline slopes down to the fourth year. Subgroup analysis showed that there was no significant difference in cumulative persistence based on gender ($p = 0.64$), age ($p = 0.17$), history of hypertension ($p = 0.36$), history of diabetes mellitus ($p = 0.05$), and history of cardiovascular diseases ($p = 0.66$). Although not significant, there was a tendency toward the decrease of cumulative persistence in male and younger patients (<59 years).

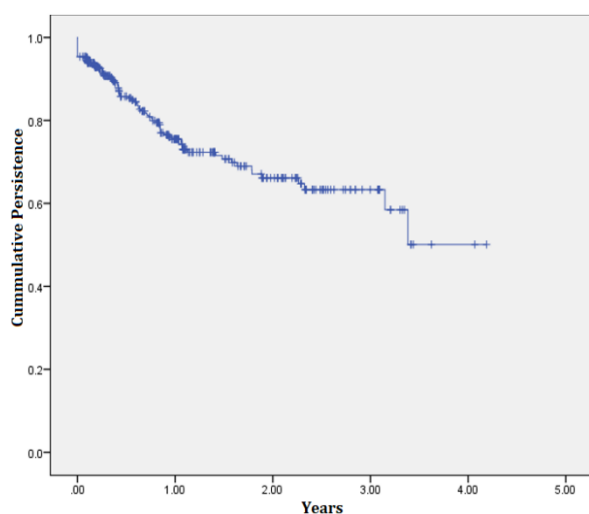


Figure 1. Persistence of lipid-lowering medication during follow-up for all patients.

Not much research has been done on the persistence of lipid-lowering drugs in ACS patients with PCI, but studies on the persistence with lipid-lowering agents in Australia among 6,859 patients with an ACS showed that as many as 93% of patients were persistent at discharge but this fell to 83% after 6 months and 74% at 2 years (Chow *et al.*, 2019). IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) study that assessed medication persistence among 17,706 patients with lipid-lowering therapy found that 5.9% of all subjects discontinued medication by day 30, 13.9% discontinued medication between day 30 and year 1, and 26.9% discontinued medication from years 1 through 7 (Navar *et al.*, 2019). A study in Japan showed persistence with lipid-lowering drugs of 35.7-63.8% at 1 year from the start of drug administration, depending on the type of lipid-modifying agents. Statins have higher persistence than other lipid-lowering medications (Wake *et al.*, 2019).

Another study about persistence with statin therapy in Hungary found that almost 80% of

patients had discontinued therapy during the first year (Kiss *et al.*, 2013). A systematic review and meta-analysis suggest that across all included studies in patients with ACS, 73.6% of women and 75.3% of men had good adherence to lipid-lowering medication (Bots *et al.*, 2021). On the other hand, a study in the Danish population (Nielsen & Nordestgaard, 2016) found that male sex was associated with early statins discontinuation. Compared to previous studies, this retrospective cohort study showed that the persistence with lipid-lowering medication on ACS patients undergoing PCI in Indonesia is similar with other countries.

Association between persistence to treatment with lipid-lowering medication and direct medical cost

The average cost per component of direct medical costs based on the persistence with lipid-lowering medication (Table II). The average direct medical costs required for the treatment of ACS patients after PCI with non-persistent lipid-lowering treatment use are higher than the persistent ones, except for the cost of consumable materials, laboratory costs, costs of other supporting examination, accommodation costs, and the cost of using medical devices, but the difference was not statistically significant. The average costs for administration ($p = 0.001$), drugs ($p = 0.005$), doctor consultation services ($p = 0.001$), and total direct medical costs ($p < 0.001$) were significantly higher in patients with non-persistence status compared to patients with persistence.

Subgroup analysis of the direct medical costs based on persistence with lipid-lowering medication and patient characteristics at baseline (Table III). All non-persistence patients with lipid-lowering drugs required a higher direct medical cost than persistent patients regardless of characteristics except in patients with other payment methods, but this finding was not statistically significant. The significant differences were more evident in non-persistence patients who were younger (<59 years), male, had a previous history of hypertension, were admitted to the hospital through the Emergency unit, and using the JKN national health insurance. This group incurred significantly higher direct medical costs compared to the persistence group.

This study shows that the direct medical costs required for the treatment of ACS patients after PCI who are non-persistent with lipid-lowering drugs are higher than for persistent patients. This can be seen in total direct medical costs and drug component costs.

Table II. Component of direct medical costs based on persistence to treatment with lipid-lowering medication.

	Average cost (IDR)			p-value
	All patients (n=267)	Persistence (n=211)	Non-persistence (n=56)	
Administration	107,792.61	100,333.91	135,564.39	0.001
Drug	4,013,147.59	3,571,192.14	5,666,060.94	0.005
Consumable materials	6,402,453.33	6,609,513.03	5,926,982.91	0.70
Medical procedures by a doctor	8,376,231.31	7,648,153.64	10,378,444.91	0.49
Medical procedures by other medical professions	815,542.28	660,673.47	1,259,499.53	0.32
Laboratory test	891,046.58	900,714.68	868,279.78	0.40
Other supporting examinations	782,876.72	808,303.14	714,659.48	0.90
Accommodation	1,521,335.07	1,555,530.05	1,452,945.10	0.75
Doctor consultation	1,563,278.11	1,412,528.51	2,127,193.29	0.001
Medical device usage	601,509.80	713,570.99	171,941.87	0.73
Other consultation	3,007,224.49	2,010,042.41	5,461,826.54	0.32
Total	10,877,269.59	9,535,209.76	15,933,959.28	< 0.001

Note: *P*-values marked with bold indicate statistically significant differences in non-persistence group compared to persistence group.

Table III. Subgroup analysis of the direct medical costs based on the persistence to treatment with lipid-lowering medication and patient characteristics at baseline.

Characteristics	Direct medical cost (IDR)		p-value
	Persistence	Non-persistence	
Age			
<59 years	10,021,774.04	17,212,753.46	0.003
≥59 years	9,136,730.39	14,458,427.53	0.03
Gender			
Male	8,579,642.78	14,597,886.84	0.002
Female	14,689,480.15	29,561,898.20	0.02
History of hypertension			
Yes	7,985,426.29	19,974,992.57	0.01
No	10,622,557.84	12,903,184.31	0.02
History of diabetes mellitus			
Yes	13,036,018.10	17,670,259.51	0.23
No	8,390,291.31	15,177,110.46	0.001
History cardiovascular disease			
Yes	11,275,357.90	13,831,819.40	0.19
No	8,743,142.33	17,013,436.51	0.001
Hospital admission			
Emergency Unit	9,924,679.11	12,700,488.54	0.002
Outpatient Clinic	7,273,774.85	26,629,285.56	0.11
Payment method			
National Health Insurance	9,446,296.41	16,166,349.32	0.001
Other payment methods	10,881,090.79	3,152,507.00	1.00

Note: *P*-values marked with bold indicate statistically significant differences in non-persistence group compared to persistence group.

Table IV. Cost-saving opportunities for persistence to treatment with lipid-lowering medication on MACE and MACCE clinical outcomes.

Persistence	Cost (IDR)	Clinical Outcome Prevention (%)	Cost Saving (IDR)
MACE			
Persistence	9,535,209.76	91.61	-996,192.41
Non-persistence	15,933,959.28	85.18	
MACCE			
Persistence	9,535,209.76	90.21	-733,103.02
Non-persistence	15,933,959.28	81.48	

Note: MACE = major adverse cardiac events, MACCE = major adverse cardiovascular and cerebrovascular events, a negative value means cost savings in the persistence group compared to non-persistence group

Previous studies that examine the association between persistence with lipid-lowering therapy and healthcare cost are limited. A study linking adherence to statin drug use with healthcare costs showed that patients who have low adherence require significantly higher total costs than those who have good adherence (Pittman *et al.*, 2011). An analysis from the United Kingdom projected that statin in secondary prevention of cardiovascular disease might bring treatment cost savings of £120 million per year with the assumption that 100% of individuals were compliant to 80% of their medication. These were projected figures to quantify the impact of poor compliance in particular indications or particular patient groups (Trueman *et al.*, 2011).

Patients who were non-persistent with lipid-lowering medication in this study had the characteristics of being older (≥ 59 years), had a history of hypertension, and using National Health Insurance to pay their healthcare spending. They require significantly higher direct medical costs than persistent patients. In addition to the costs involved in the management of cardiovascular events in patients with ACS after PCI, the presence of comorbidities in older patients, such as hypertension, can increase the cost of care. The occurrence of non-persistent patients with the JKN national health insurance financing who require significantly higher direct medical costs than other payment methods is probably caused by the reimbursement system that provides healthcare services for all medication and procedures according to the indications outlined by the Indonesian Healthcare and Social Security Agency (*Badan Penyelenggara Jaminan Sosial Kesehatan*). Meanwhile, other payment methods are highly dependent on the premiums paid by the patient/insurance client and out-of-pocket expenses so the costs tend to be smaller.

Cost-saving opportunities from persistence to treatment with lipid-lowering agents

Persistence with lipid-lowering drugs can provide cost savings of IDR 996,192.41 in preventing one MACE and IDR 733,103.02 in preventing one MACCE event (Table IV). Research about cost-saving or cost-effectiveness from persistence to treatment with lipid-lowering drugs, especially in patients with ACS after PCI is still limited. An analysis from a claims database reported that patients with high triglycerides were associated with higher healthcare costs (Toth *et al.*, 2018). Another analysis from the US found that treatment with generic simvastatin appears to be cost-effective with a daily cost of USD 1 for 40 mg generic simvastatin. The estimated costs of preventing a vascular death during the study ranged from a net saving of USD \$1,300 among participants with a 42% 5-year risk of heart attack, stroke, or revascularization procedure (major vascular event; equivalent to a 40% 10-year risk of heart attack or coronary death) to a net cost of USD \$216,500 among those with a 5-year 12% risk (10% with 10-year risk of heart attack or coronary death) (Mihaylova *et al.*, 2009). A cost-effectiveness study from Taiwan found that statin use as a secondary prevention strategy in coronary arterial disease patients with a baseline LDL-cholesterol level of 70-100 mg/dl could be cost-effective given the health benefits in preventing cardiovascular events. Statin therapy can be considered 'highly cost-effective' in Taiwan since the incremental cost-effectiveness ratio (ICER) was USD \$20,288 per quality-adjusted life-year (QALY) gained, far below Taiwan GDP per capita in 2017 which is US\$24,329 (Lin *et al.*, 2020). An economic evaluation in the Philippines reported that simvastatin was the most cost-effective option if the cost of the lower-priced generic counterpart was used in the analysis. However, if the cost of the higher-priced innovator drugs was used except for

pravastatin (of which there was just one brand available), it was found that pravastatin was the most cost-effective therapy. The incremental cost of using atorvastatin either over simvastatin or over pravastatin ranged from about PHP 65,000 to PHP 130,000 for every QALY gained (Tumanan-Mendoza & Mendoza, 2013). These results provide another perspective for cost-saving opportunities from persistence to treatment with lipid-modifying agents in Indonesia considering the varied willingness-to-pay threshold between countries, with Indonesian GDP in 2020 reported at USD \$3,911.70 (The Central Bureau of Statistics Indonesia, 2021). This study provides real-world data to improve secondary prevention in cardiovascular disease patients and give prominence to the substantial roles of medication persistence in patients with ACS after PCI. Further studies about cost-effectiveness of persistence to treatment with lipid-lowering agents are needed to calculate the benefits in the Indonesia setting from a payer perspective.

The limitations of this study were due to the medical records and administrative medical claim data used. There is the possibility of incomplete, inaccurate, or missing information about patient conditions that may be relevant for the study and may limit the generalizability of the results. Another limitation related to claim data is the possibility of billing and coding errors.

CONCLUSIONS

In ACS patients undergoing PCI, the total direct medical costs and drug costs incurred by patients who were persistent to treatment with lipid-lowering agents were significantly lower compared to non-persistent patients. Persistence to treatment with lipid-lowering drugs can provide cost savings of IDR 996,192.41 in preventing one MACE event and IDR 733,103.02 in preventing one MACCE event.

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