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Persistence with Antiplatelet and Risk of Major Adverse Cardiac and Cerebrovascular Events in Acute Coronary Syndrome Patients after Percutaneous Coronary Intervention in Indonesia: A Retrospective Cohort Study

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Abstract

BACKGROUND: Acute coronary syndrome (ACS) is a life-threatening condition that carries high risk of recurrent cardiovascular events and death. Persistence with treatment is known to reduce morbidity and mortality in patients with ACS.

AIM: This study focuses on ACS patients undergoing their first percutaneous coronary intervention (PCI) to investigate the association between persistence with antiplatelet therapy and clinical outcomes.

MATERIALS AND METHODS: A retrospective cohort study with 2 years of follow-up was conducted with 367 patients recruited. Patients were deemed as having persistence with antiplatelet therapy (WHO ATC code: B0A1C), if the gap between prescriptions was ≤30 days. The clinical outcomes were defined as a composite of major adverse cardiac event (MACE), major adverse cardiovascular and cerebrovascular events (MACCE), myocardial infarction, recurrent PCI, stroke, all-cause death, cardiovascular death, and hospitalization.

RESULTS: Cumulative persistence with antiplatelet showed that 72.3% of all ACS patients were still taking antiplatelet 1 year after PCI. Persistence to treatment with antiplatelet therapy can be used as a predictor of MACE or MACCE, because it was associated with recurrent PCI (RR 3.09, 95% CI = 1.18−8.05). History of cardiovascular disease in non-persistence patients was associated with increased risk of MACE (RR 4.90 95% CI = 1.37−17.48) and MACCE (RR 3.67 95% CI = 1.12−11.98) events.

CONCLUSION: After PCI, not all ACS patients continued taking their drug exactly as prescribed. Our study indicates that among ACS patients who underwent their first PCI, non-persistence with antiplatelet therapy might lead to worse clinical outcomes. This data will help promote secondary prevention among ACS patients after PCI.

Introduction

Acute coronary syndrome (ACS) is a life-threatening condition that carries a high risk of recurrent cardiovascular events and death [1]. This condition may worsen in the presence of comorbidities such as diabetes mellitus, hypertension, dyslipidemia, obesity, hematological diseases, and poor lifestyle. A long-term pharmacological approach is essential for secondary prevention. It is therefore vital to ensure the patient's therapy persistence in this long-term therapy management. The treatment persistence is known to reduce disease morbidity and mortality substantially [2], [3], [4]. This study focuses on the persistence of antiplatelet therapy on ACS patients undergoing their first PCI to investigate the association between persistence with antiplatelet therapy and clinical outcomes. This data will be helpful for policymakers in reviewing ACS management and improve secondary prevention.

Materials and Methods

A retrospective cohort study was conducted to assess the association between persistence with antiplatelet and clinical outcomes in ACS patients undergoing PCI. We used existing medical record data from five hospitals: Dr. Sardjito Hospital, Dr. Moewardi Hospital, Hardjolukito Hospital, Dr. Karyadi Hospital, and Panti Rapih Hospital. Data were collected from

January 2019 to February 2020. The patients' follow-up was based on data available from the medical records.

The subjects of this study were ACS patients who underwent their first PCI. 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 were as follows: (1) incomplete or unavailable medical record data; (2) patients with pregnancy; (3) patients diagnosed with chronic kidney disease; and (4) patients diagnosed with cancer. Patients were defined as having persistence with antiplatelet (WHO ATC code: B0A1C), if the gap between prescriptions was ≤ 30 days. Clinical outcomes were defined as a composite of major adverse cardiac event (MACE), major adverse cardiovascular and cerebrovascular events (MACCE), myocardial infarction, recurrent PCI, stroke, all-cause death, cardiovascular death, and hospitalization. MACE consists of all-cause death, myocardial infarction, and recurrent PCI. MACCE is defined as a composite of recurrent PCI, myocardial infarction, stroke, or all-cause death.

Baseline characteristics of ACS patients undergoing PCI were analyzed descriptively. Categorical data are presented in frequency and proportion, while continuous data are expressed as mean and standard deviation (SD). Persistence to treatment with antiplatelet is presented with the Kaplan–Meier method and stratified by the history of cardiovascular diseases followed by a log-rank test to see if any differences exist.

Association between persistence to treatment with clinical outcomes (MACE, MACCE, myocardial infarction, recurrent PCI, stroke, all-cause death, cardiovascular death, and hospitalization) was analyzed by logistic regression adjusted for age and gender. Subgroup analysis was conducted to evaluate the relationship between treatment persistence and clinical outcomes based on baseline characteristics. The association between non-persistence with antiplatelet and clinical outcomes was reported in the form of relative risk (RR) with 95% confidence interval (CI) and $p < 0.05$ set as a significant result. Statistical analysis was performed with Microsoft Excel and SPSS Statistics 23 Version. This research protocol had received ethical approval from the Medical and Health Research Ethics Committee (MHREC) of the Faculty of Medicine, Public Health and Nursing of Universitas Gadjah Mada. This was an observational study using secondary data from medical records so the informed consent was waived.

Results

Baseline characteristics

ACS patients who underwent PCI that met the inclusion and exclusion criteria in the study were 367 people. Table 1 shows that most of the patients were male (85.0%), with a mean age of 58.8 ± 9.7 years. Most of the patients had an education level of high school or below (62.4%). As many as, 24.0−36.5% of patients had comorbidities (diabetes mellitus, hypertension, and cardiovascular diseases). At baseline, the patients' mean systolic blood pressure was 131.1 ± 23.5 mmHg and the mean diastolic blood pressure was 80.9 ± 15.1 mmHg. This measurement conforms to the prehypertension category. The majority of the patients (78.5%) were admitted to the hospital through the emergency unit. Most patients showed persistence to treatment with antiplatelet (74.7%).

Table 1: The baseline characteristics of acute coronary syndrome patients undergoing percutaneous coronary intervention

Characteristics	Total (n = 367), n (%)	Antiplatelet	
		p (n = 274, 74.7%), n (%)	NP (n = 93, 25.3%), n (%)
Gender			
Male	312 (85.0)	230 (83.9)	82 (88.2)
Female	55 (15.0)	44 (16.1)	11 (11.8)
Age (years), mean ± SD	58.8 ± 9.7	59.1 ± 9.9	58.1 ± 9.1
Education level			
High school or below	229 (62.4)	170 (62.0)	59 (63.5)
Higher than high school	82 (22.3)	63 (23.0)	19 (20.4)
No data	56 (15.3)	41 (15.0)	15 (16.1)
Comorbidities			
Diabetes mellitus	88 (24.0)	60 (21.9)	28 (30.1)
Hypertension	134 (36.5)	102 (37.2)	32 (34.4)
Cardiovascular diseases	106 (28.9)	80 (29.2)	26 (28.0)
Cerebrovascular diseases	5 (1.4)	4 (1.5)	1 (1.1)
Respiratory diseases	16 (4.4)	8 (2.9)	8 (8.6)
Gastrointestinal diseases	21 (5.7)	14 (5.1)	7 (7.5)
Blood pressure, mean ± SD			
Systolic (mmHg)	131.1 ± 23.5	130.8 ± 22.9	132.0 ± 25.4
Diastolic (mmHg)	80.9 ± 15.1	80.7 ± 15.1	81.4 ± 15.3
Hospital admission			
Emergency unit	288 (78.5)	221 (80.7)	67 (72.0)
Outpatient clinic	78 (21.3)	52 (19.0)	26 (28.0)
No data	1 (0.3)	1 (0.4)	0

P: Persistence, NP: Non-persistence, SD: Standard deviation.

Persistence with antiplatelet

The median follow-up duration for antiplatelet therapy was 8.3 (IQR: 2.2−17.2) months. The Kaplan–Meier curve (Figure 1) shows a rapid (27.7%) decline in cumulative persistence of antiplatelet use in the 1st year before declining gradually until the 4th year. The

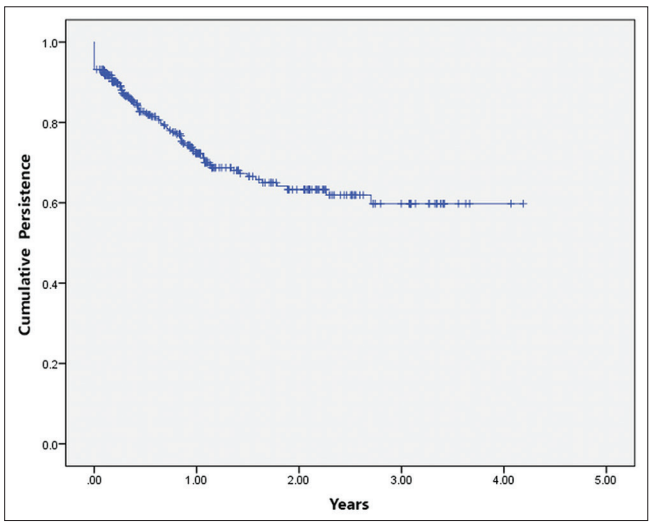

Figure 1: Persistence with antiplatelet during follow-up for all patients

subgroup analysis, in Figure 2, shows no significant difference in cumulative persistence based on the history of cardiovascular diseases (p = 0.81).

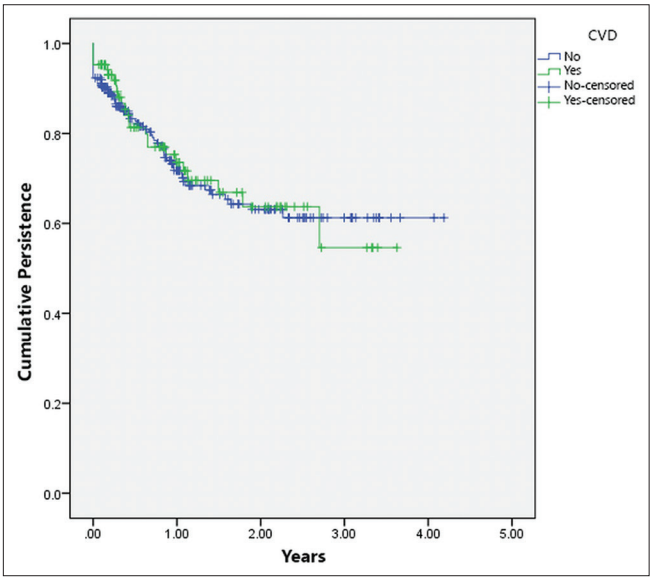

Figure 2: Persistence with antiplatelet during follow-up; a subgroup analysis by the history of cardiovascular diseases

Table 2 shows that non-persistence with antiplatelet was associated with an increased risk of adverse clinical outcomes, namely, MACE, MACCE, recurrent PCI, stroke, and hospitalization. There was a tendency for an increased risk of myocardial infarction in patients who persisted with antiplatelet therapy, but this was not significant. A significant association was found only between non-persistence with antiplatelet therapy and recurrent PCI (RR 3.09, 95% CI = 1.18−8.05).

Table 2: Association between non-persistence with antiplatelet and clinical outcomes

Clinical outcomes	Event		Crude RR (95% CI)	Adjusted RR (95% CI)*
	P	NP		
MACE	23/274	13/93	1.77 (0.86–3.66)	1.72 (0.83–3.57)
MACCE	27/274	16/93	1.90 (0.97–3.71)	1.87 (0.96–3.66)
Myocardial infarction	14/274	4/93	0.83 (0.27–2.60)	0.80 (0.25–2.50)
Recurrent PCI	9/274	9/93	3.15 (1.21–8.21)	**3.09 (1.18–8.05)**
Stroke	7/274	3/93	1.27 (0.32–5.02)	1.31 (0.33–5.20)
Death	1/274	0/93	Not analyzed	Not analyzed
Death because of cardiovascular diseases	1/274	0/93	Not analyzed	Not analyzed
Hospitalization	52/274	23/93	1.40 (0.80–2.45)	1.39 (0.79–2.45)

*Adjusted to age and gender. Relative risk marked with bold indicate statistically significant differences in NP group compared to *P* group. P: Persistence, NP: Non-persistence, RR: Relative risk, CI: Confidence interval, MACE: Major adverse cardiac events, MACCE: Major adverse cardiovascular and cerebrovascular events, PCI: Percutaneous coronary intervention.

Table 3 shows that several characteristics tend to increase the adjusted relative risk (RR) value for MACE, as shown in Table 2. Two factors that significantly increase the adjusted RR for MACE are the history of cardiovascular diseases (RR 4.90, 95% CI = 1.37−17.48) and hospital admission through outpatient clinic (RR 4.26, 95% CI = 1.01−18.01).

Table 4 shows that several characteristics tend to increase the adjusted RR value for MACCE, as shown in Table 2. Four factors that significantly increase the adjusted RR for MACCE are education level of high school or below (RR 2.44, 95% CI = 1.07−5.55), hospital admission through the outpatient clinic (RR 4.26, 95% CI = 1.01−18.01), history of cardiovascular diseases (RR 3.67, 95% CI = 1.12−11.98), and diastolic blood pressure of ≥ 80 mmHg (RR 2.60, 95% CI = 1.12−6.06).

Table 3: The adjusted relative risk of non-persistence with antiplatelet and major adverse cardiac events

Characteristics	Event		Crude RR (95% CI)	Adjusted RR (95% CI)*
	P	NP		
Education level				
High school or below	13/170	9/59	2.17 (0.88–5.39)	2.16 (0.85–5.40)
Higher than high school	6/63	2/19	1.12 (0.21–6.05)	1.13 (0.21–6.24)
Hospital admission				
Emergency unit	19/221	7/67	1.24 (0.50–3.09)	1.22 (0.49–3.06)
Outpatient clinic	4/52	6/26	3.60 (0.92–14.15)	**4.26 (1.01–18.01)**
History of hypertension				
Yes	8/102	6/32	2.71 (0.86–8.51)	2.63 (0.83–8.31)
No	15/172	7/61	1.36 (0.52–3.50	1.28 (0.49–3.33)
History of diabetes mellitus				
Yes	7/60	6/28	2.06 (0.62–6.84)	2.08 (0.62–6.95)
No	16/214	7/65	1.49 (0.59–3.80)	1.38 (0.54–3.52)
History of cardiovascular diseases				
Yes	5/80	7/26	5.53 (1.58–19.35)	**4.90 (1.37–17.48)**
No	18/194	6/67	0.96 (0.36–2.53)	0.97 (0.37–2.58)
Systolic BP (mmHg)				
≥130	10/148	6/48	1.97 (0.68–5.74)	1.93 (0.66–5.70)
<130	13/125	7/45	1.59 (0.59–4.27)	1.57 (0.58–4.25)
Diastolic BP (mmHg)				
≥80	13/160	9/658	2.08 (0.84–5.16)	1.95 (0.78–4.88)
<80	10/113	4/35	1.33 (0.39–4.53)	1.22 (0.35–4.24)

*Adjusted to age and gender. Relative risk marked with bold indicate statistically significant differences in NP group compared to *P* group. CI: Confidence interval, NP: Non-persistence, P: Persistence, RR: Relative risk, BP: Blood pressure.

Table 4: The adjusted relative risk of non-persistence with antiplatelet and MACCE

Characteristics	Event		Crude RR (95% CI)	Adjusted RR (95% CI)*
	P	NP		
Education level				
High school or below	16/170	12/59	2.46 (1.09–5.56)	**2.44 (1.07–5.55)**
Higher than high school	6/63	2/19	1.12 (0.21–6.05)	1.13 (0.21–6.24)
Hospital admission				
Emergency unit	23/221	10/67	1.51 (0.68–3.36)	1.51 (0.68–3.38)
Outpatient clinic	4/52	6/26	3.60 (0.92–14.15)	**4.26 (1.01–18.01)**
History of hypertension				
Yes	11/102	7/32	2.32 (0.81–6.59)	2.28 (0.80–6.49)
No	16/172	9/61	1.69 (0.70–4.05)	1.63 (0.68–3.93)
History of diabetes mellitus				
Yes	10/60	8/28	2.00 (0.69–5.80)	2.05 (0.70–6.04)
No	17/214	8/65	1.63 (0.67–3.96)	1.54 (0.63–3.76)
History of cardiovascular diseases				
Yes	7/80	7/26	3.84 (1.20–12.29)	**3.67 (1.12–11.98)**
No	20/194	9/67	1.35 (0.58–3.13)	1.36 (0.58–3.17)
Systolic BP (mmHg)				
≥130	11/148	8/48	2.49 (0.94–6.61)	2.46 (0.92–6.57)
<130	16/125	8/45	1.47 (0.58–3.72)	1.46 (0.58–3.70)
Diastolic BP (mmHg)				
≥80	14/160	12/58	2.72 (1.17–6.30)	**2.60 (1.12–6.06)**
<80	13/113	4/35	0.99 (0.30–3.26)	0.92 (0.28–3.06)

*Adjusted to age and gender. Relative risk marked with bold indicate statistically significant differences in NP group compared to *P* group. CI: Confidence interval, NP: Non-persistence, P: Persistence, RR: Relative risk, BP: Blood pressure.

Discussion

The results of this retrospective cohort study showed that persistence to treatment with antiplatelet decreased with time. Non-persistence use of antiplatelet therapy was significantly associated with an increased risk of recurrent PCI.

Cumulative persistence of antiplatelet use decreased rapidly to 72.3% in the 1st year, before gradually declined until the 4th year. Compared with other countries, persistence to treatment with antiplatelet in this study is almost comparable to that of antiplatelet persistence in Catalonia (Spain), which decreased to

73% at 1 year after PCI [5]. A study in Finland also showed a similar trend, with ~75% of ACS patients still taking antiplatelet drugs at 1 year after the diagnosis was made [6]. On the other hand, a study in Belgium with 295 ACS patients found that treatment persistence with oral antiplatelet after an ACS at 360 days from hospital discharge was 73% [7]. Persistence with antiplatelet drug use in the Netherlands tends to be higher, that is, 84.0% at 1 year after myocardial infarction [8]. Another study in French reported 50.9% persistence with dual antiplatelet therapy during a 12-month period after hospitalization in patients admitted with myocardial infarction and PCI [9]. Another report from Vietnam National Heart Institute also showed similar results on persistence with antiplatelet therapy at 46.29% after 12 months of hospital discharge in patients with myocardial infarction and PCI [10]. Meanwhile, in China, persistence with antiplatelet therapy was found to be lower. Nearly 85% of patients had discontinued antiplatelet by the end of the study, with a time-to-discontinuation of 117.4 ± 119.7 days [11].

However, a subgroup analysis done in this study showed that the cumulative persistence of antiplatelet therapy did not significantly affected by the history of cardiovascular diseases. The results of this study are different from the previous studies, in which older age, female gender, history of hypertension, history of hyperlipidemia, history of atrial fibrillation, and history of ACS event were associated with increased risk of non-persistence with antiplatelet therapy [5], [6]. Even though the history of cardiovascular diseases did not significantly affect antiplatelet persistence in this study, it still needs to be considered in the management of ACS patients undergoing PCI. A study in Poland had found that previous diagnosis of coronary artery disease, previous myocardial infarction, prior PCI, or coronary artery bypass graft was associated with the decrease in persistence to treatment [12]. Another study with clopidogrel, an antiplatelet drug, reported that non-persistence was significantly associated with prior use of clopidogrel, prior all-cause hospitalization, PCI without stenting, chronic pulmonary disease, younger age, and diabetes [13].

This study indicated that non-persistence with antiplatelet was associated with the incidence of recurrent PCI. The results of this study were consistent with the results of a study on a population of PCI patients in the United States from the PARIS Registry, which showed that discontinuation of dual antiplatelet therapy (DAPT) for > 30 days after PCI was associated with increased MACE (RR 1.61, 95% CI = 1.20-2.17) [14]. Another insight highlighted from PARIS Registry was that in patients with DAPT disruption due to non-compliance, higher MACE rates [hazard ratio (HR):1.73, 95% CI = 1.17–2.54] were found [15]. A study in China also added that non-persistence with guideline-recommended medications was associated with a 2-fold higher odds of MACEs [16]. Studies in the PARIS Registry also showed that in the context of time after PCI, they saw that the risk of adverse cardiac events was highest in the first 6 months after intervention [17].

The previous studies have also shown several characteristics that are significantly associated with recurrent cardiovascular events in STEMI or coronary artery disease patients undergoing PCI, such as the history of previous cardiovascular diseases, history of diabetes mellitus, and history of hypertension, older age, smoking, stent length, and hyperlipidemia[18], [19], [20], [21], [22]. These results were similar to those found in this study that a history of cardiovascular diseases increased the adjusted RR for MACE and MACCE events.

The present study does have some limitations. One major limitation is due to the medical record data used in this study. There were possibilities of coding errors and incomplete information about patients' characteristics that might be relevant for the study, and thus might limit the generalizability of the results.

Conclusion

After PCI, not all ACS patients continued taking their drug exactly as prescribed. This study showed that only 72.3% of ACS patients continued taking antiplatelet 1 year after PCI. Patients who were non-persistent with antiplatelet therapy had a relative risk of recurrent PCI 3.09 times higher than those who were persistent with antiplatelet therapy. Persistence with antiplatelet can be a predictor of clinical outcomes in ACS patients undergoing their first PCI. Although there were some limitations, this study provides real-world evidence that assists in discovering the association between persistence with antiplatelet therapy and clinical outcomes, which may promote secondary prevention for ACS patients after PCI.

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