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Persistence to Antihypertensive and Clinical Outcomes in Acute Coronary Syndrome Patients after Percutaneous Coronary Intervention

Erna Kristin[1], Lucia Kris Dinarti[2], Ratih Puspita Febrinasari[3]*, Woro Rukmi Pratiwi[1], Alfi Yasmina[4] and Sudi Indra Jaya[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 Sebelas Maret, Kentingan, 57126, Surakarta, Indonesia
4. Department of Pharmacology, Faculty of Medicine, Universitas Lambung Mangkurat, 70123 Banjarmasin, Indonesia

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*Corresponding author
Ratih Puspita Febrinasari

Email:
ratihpuspita@staff.uns.ac.id

ABSTRACT

Acute coronary syndrome (ACS) is a life-threatening condition that carries a high risk of recurrent cardiovascular events and death. Persistence to treatment is known to reduce disease morbidity and mortality in patients with ACS. In this study, we focus on ACS patients undergoing their first percutaneous coronary intervention (PCI) to investigate the association between persistence to antihypertensive therapy and clinical outcomes. A retrospective cohort study with two years of follow-up was conducted with 367 patients recruited. Patients were deemed as having the persistence to antihypertensive therapy (WHO ATC Code C02, C03, C07, C08, C09) if the gap between prescriptions was ≤ 30 days. The clinical outcomes were defined as a composite of major adverse cardiac events (MACE), major adverse cardiovascular and cerebrovascular events (MACCE), myocardial infarction, recurrent PCI, stroke, all-cause death, cardiovascular death, and hospitalization. Cumulative persistence to antihypertensive showed 72.3% of ACS patients still taking antihypertensive one year after PCI. Persistence to treatment with antihypertensive therapy can be used as a predictor of MACE or MACCE because it was associated with recurrent PCI (RR 1.94, 95% CI = 1.02-3.71). Our study indicates that among ACS patients undergoing their first PCI, non-persistence to antihypertensive therapy may lead to worse clinical outcomes. This data will be useful in promoting secondary prevention in ACS patients after PCI.

Keywords: antihypertensive, persistence to treatment, clinical outcomes, percutaneous coronary intervention

INTRODUCTION

Acute coronary syndrome (ACS) is a life-threatening condition that carries a high risk of recurrent cardiovascular events and death (Qvarnström *et al.*, 2016). This condition may worsen due to comorbidities such as diabetes mellitus, hypertension, dyslipidemia, obesity, hematological diseases, and poor lifestyle. A long-term pharmacological approach is very important for secondary prevention. It is therefore important to ensure the patient's therapy persistence in this long-term therapy management. Treatment persistence is known to reduce disease morbidity and mortality substantially (Grimmsmann *et al.*, 2014; Ah *et al.*, 2015; Si S *et al.*, 2019). A study from Korean nationwide medical insurance data reported that beta-blocker therapy for ≥1 year in patients who underwent revascularization for myocardial infarction (MI) was associated with reduced mortality (Kim *et al.*, 2020). A multi-center study in Australia found that the use of angiotensin-

converting enzyme inhibitors (ACEi) or angiotensin II-receptor blockers (ARBs) was associated with significant long-term survival benefits in patient's post-PCI for MI (Prosser *et al.*, 2022). This study focused on the persistence of antihypertensive therapy in ACS patients undergoing their first PCI to investigate the association between the persistence of antihypertensive therapy and clinical outcomes. This data will be useful for policymakers in reviewing ACS management and improving secondary prevention.

MATERIALS AND METHODS

This retrospective cohort study assessed the association between persistence to antihypertensive and clinical outcomes in ACS patients undergoing PCI. We utilize existing medical record data from five hospitals: Dr. Sardjito Hospital, Dr. Moewardi Hospital, Hardjolukito Hospital, Dr. Karyadi Hospital, and Panti Rapih Hospital. The data was collected between January 2019 and February 2020.

The investigation was conducted on ACS patients who underwent their first PCI. Inclusion criteria for the study were: (1) 18 years of age or older; (2) Patients having PCI procedures for the first time. The exclusion criteria for the study were as follows: (1) Medical record data is incomplete or unavailable; (2) Patients with pregnancy; (3) Patients diagnosed with chronic kidney disease; and (4) Patients diagnosed with cancer. Persistence to antihypertensive was measured using the gaps between refills method. Patients were defined as having the persistence to antihypertensive if the gap between prescriptions is ≤ 30 days. Medicines included in this study were defined using WHO ATC Code C02 (antihypertensives), C03 (diuretics), C07 (Beta blocking agents), C08 (calcium channel blockers), and C09 (agents acting on the renin-angiotensin system).

Clinical outcomes were defined as a composite of major adverse cardiac events (MACE), major adverse cardiovascular and cerebrovascular events (MACCE), myocardial infarction (MI), recurrent PCI, stroke, all-cause death, cardiovascular death, and hospitalization. MACE consists of all-cause death, myocardial infarction (MI), and recurrent PCI. MACCE is defined as a composite of recurrent PCI, myocardial infarction, stroke, or all-cause death.

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

The 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 carried out to evaluate the relationship between treatment persistence and clinical outcomes based on baseline characteristics. Statistical analysis was performed with Microsoft Excel and SPSS Statistics 23 Version. This research protocol has received ethical approval from the Medical and Health Research Ethics Committee (MHREC), Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, with reference number: KE/FK/1140/EC/2018.

RESULTS AND DISCUSSION

Baseline Characteristics

ACS patients who underwent PCI that met the inclusion and exclusion n criteria in the study were 367 people. That most patients were male (83.5%), with a mean age of 58.1 ± 9.0 years (Table I). Most patients had an education level of high school or below (61.7%). As many as 21.0-44.0% of patients had comorbidities (diabetes mellitus, hypertension, and cardiovascular diseases). At baseline, the patient's mean systolic blood pressure was 131.6 ± 23.2 mmHg, and mean diastolic blood pressure at 81.3 ± 160 mmHg. This blood pressure level conforms to the prehypertension category for patients without a history of hypertension. For 134 patients with a history of hypertension who used antihypertensive regularly, their blood pressure is under control due to the medicines given. Most patients (80.2%) were admitted to the hospital through the Emergency Unit. Most patients show persistence to treatment with antihypertensive (74.7 %).

Persistence with antihypertensive

The median follow-up duration for antihypertensive therapy was 9.4 (IQR: 2.2-17.8) months. The Kaplan-Meier curve (Figure 1) shows that there was a rapid (27.7%) decline in cumulative persistence of antihypertensive use in the first year and then declined gradually until the fourth year.

Table I. Baseline characteristics of the subjects

Characteristics	Total (n = 367) n (%)	Antihypertensive	
		P (n = 274, 74.7%) n (%)	NP (n = 93, 25.3%) n (%)
Gender			
Males	312 (85.0)	207 (83.5)	105 (88.2)
Females	55 (15.0)	41 (16.5)	14 (11.8)
Age (years), Mean±SD	58.8 (9.7)	59.2 (10.0)	58.1 (9.0)
Education level			
High school or below	229 (62.4)	153 (61.7)	77 (63.9)
Higher than high school	82 (22.3)	58 (23.4)	24 (20.1)
No data	56 (15.3)	37 (14.9)	19 (16.0)
Comorbidities			
Diabetes mellitus	88 (24.0)	57 (23.0)	31 (26.1)
Hypertension	134 (36.5)	90 (36.3)	44 (37.0)
Cardiovascular diseases	106 (28.9)	71 (28.6)	35 (29.4)
Cerebrovascular diseases	5 (1.4)	4 (1.6)	1 (0.8)
Respiratory diseases	16 (4.4)	9 (3.6)	7 (5.9)
Gastrointestinal diseases	21 (5.7)	11 (4.4)	10 (8.4)
Blood Pressure			
Systolic (mmHg), Mean±SD (n=369)	131.1 (23.5)	131.6 (23.2)	130.1 (24.2)
Diastolic (mmHg), Mean±SD (n=369)	80.9 (15.1)	81.3 (16.0)	80.0 (13.1)
Hospital admission			
Emergency Unit	288 (78.5)	199 (80.2)	89 (74.8)
Outpatient Clinic	78 (21.3)	48 (19.4)	30 (25.2)
No data	1 (0.3)	1 (0.4)	0 (0.0)

P = persistence, NP = non-persistence, SD = standard deviation.

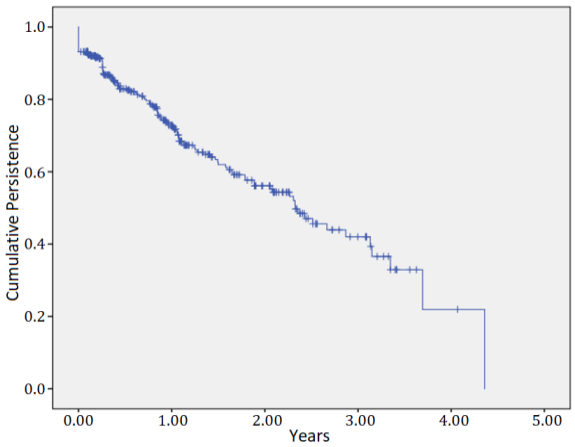

Figure 1. Persistence with antihypertensive during follow-up for all patients.

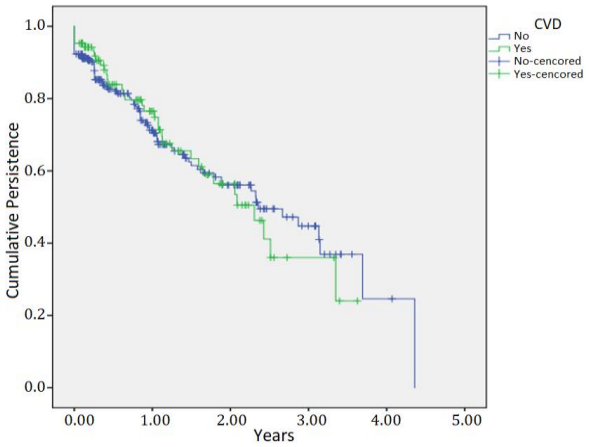

Figure 2. Persistence with antihypertensive during follow-up, subgroup analysis by the history of CVD (cardiovascular diseases).

Subgroup analysis (Figure 2) was no significant difference in cumulative persistence based on the history of cardiovascular diseases (p = 0.95).

Non-persistence with antihypertensive was associated with increased risk of clinical outcomes (Table II), namely MACE, MACCE, recurrent PCI, stroke, and hospitalization. A significant association was found in MACCE (RR 1.94, 95%CI = 1.02-3.71) and recurrent PCI (RR 2.68, 95%CI = 1.03-6.99), while the tendency of association with MACE, stroke, and hospitalization was not significant.

Table II. Association between non-persistence with antihypertensive and clinical outcomes

Clinical Outcomes	Event		Crude RR (95%CI)	Adjusted RR (95%CI)*
	P	NP		
MACE	19/248	17/119	2.01 (1.00-4.02)	1.95 (0.97-3.92)
MACCE	23/248	20/119	1.98 (1.04-3.76)	**1.94 (1.02-3.71)**
Myocardial infarction	11/248	7/119	1.35 (0.51-3.57)	1.29 (0.48-3.44)
Recurrent PCI	8/248	10/119	2.75 (1.06-7.17)	**2.68 (1.03-6.99)**
Stroke	7/248	3/119	0.89 (0.23-3.51)	0.92 (0.23-3.64)
Death	1/248	0/119	Not analyzed	Not analyzed
Death because of CVD	1/248	0/119	Not analyzed	Not analyzed
Hospitalization	50/248	25/119	1.05 (0.61-1.81)	1.04 (0.61-1.79)

*Adjusted to age and gender. 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. Bold indicates significance at the $p < 0.05$ level, CVD = cardiovascular diseases.

Table III. The adjusted relative risk of non-persistence with antihypertensive and MACE

Characteristics	Event		Crude RR (95%CI)	Adjusted RR (95%CI)*
	P	NP		
Education level				
High school or below	12/153	10/76	1.78 (0.73-4.33)	1.75 (0.71-4.32)
Higher than high school	5/58	3/24	1.51 (0.33-6.91)	1.52 (0.33-7.00)
Hospital admission				
Emergency Unit	15/199	11/89	1.73 (0.76-3.93)	1.68 (0.73-3.86)
Outpatient Clinic	4/48	6/30	2.75 (0.71-10.71)	2.98 (0.75-11.88)
History of hypertension				
Yes	7/90	7/44	2.24 (0.73-6.85)	2.18 (0.71-6.70)
No	12/158	10/75	1.87 (0.77-4.55)	1.78 (0.73-4.36)
History of diabetes mellitus				
Yes	4/57	9/31	5.42 (1.51-19.46)	**5.51 (1.52-19.97)**
No	15/191	8/88	1.17 (0.48-2.88)	1.08 (0.44-2.67)
History of cardiovascular disease				
Yes	5/71	7/35	3.30 (0.96-11.29)	2.64 (0.76-9.15)
No	14/177	10/84	1.57 (0.67-3.71)	1.59 (0.67-3.77)
Systolic BP				
≥ 130 mmHg	9/137	7/59	1.91 (0.68-5.41)	1.88 (0.66-5.36)
< 130 mmHg	10/110	10/60	2.00 (0.78-5.12)	1.93 (0.75-4.97)
Diastolic BP				
≥ 80 mmHg	10/145	12/73	2.66 (1.09-6.48)	**2.55 (1.04-6.26)**
< 80 mmHg	9/102	5/46	1.26 (0.40-3.99)	1.13 (0.35-3.61)

* Adjusted to age and gender. CI = confidence interval, NP = non-persistence, P = persistence, RR = relative risk, BP = blood pressure. Bold indicates significance at the $p < 0.05$ level.

Some of several characteristics tend to increase the adjusted relative risk (RR) value for MACE (Table III). Two factors that significantly increased the adjusted RR for MACE were the history of diabetes mellitus (RR 5.51, 95%CI = 1.52-19.97) and diastolic blood pressure ≥ 80 mmHg (RR 2.55, 95% CI = 0.35-3.61).

Some of several characteristics tend to increase the adjusted RR value for MACCE (Table III). Two factors that significantly increased the adjusted RR for MACCE were a history of diabetes mellitus (RR 4.03, 95%CI = 1.35-12.03) and diastolic blood pressure ≥ 80 mmHg (RR 3.06, 95% CI = 1.32-7.11).

This study aimed to investigate the association between persistence to anti-hypertensive therapy and clinical outcomes in ACS patients undergoing their first PCI. The results of this retrospective cohort study showed that persistence to treatment with antihypertensive decreased over time with a rapid (27.7%) decline in cumulative at the first year.

Table IV**.** The adjusted relative risk of non-persistence to antihypertensive and MACCE

Characteristics	Event		Crude RR (95%CI)	Adjusted RR (95%CI)*
	P	NP		
Education level				
High school or below	15/153	13/76	1.90 (0.85-4.23)	1.88 (0.84-4.21)
Higher than high school	5/58	3/24	1.51 (0.33-6.91)	1.52 (0.33-7.00)
Hospital admission				
Emergency Unit	19/199	14/89	1.77 (0.84-3.71)	1.76 (0.83-3.72)
Outpatient Clinic	4/48	6/30	2.75 (0.71-10.71)	2.98 (0.75-11.88)
History of hypertension				
Yes	10/90	8/44	1.78 (0.65-4.88)	1.75 (0.64-4.82)
No	13/158	12/75	2.12 (0.92-4.91)	2.06 (0.89-4.80)
History of diabetes mellitus				
Yes	7/57	11/31	3.93 (1.33-11.57)	**4.03 (1.35-12.03)**
No	16/191	9/88	1.25 (0.53-2.94)	1.17 (0.49-2.78)
History of cardiovascular disease				
Yes	7/71	7/35	2.29 (0.73-7.13)	2.09 (0.65-6.74)
No	16/177	13/84	1.84 (0.84-4.03)	1.86 (0.85-4.08)
Systolic BP				
≥ 130 mmHg	10/137	9/59	2.29 (0.88-5.96)	2.26 (0.86-5.91)
< 130 mmHg	13/110	11/60	1.67 (0.70-4.01)	1.65 (0.68-3.96)
Diastolic BP				
≥ 80 mmHg	11/145	15/73	3.15 (1.36-7.27)	**3.06 (1.32-7.11)**
< 80 mmHg	12/102	5/46	0.91 (0.30-2.77)	0.84 (0.28-2.57)

*Adjusted to age and gender. CI = confidence interval, NP = non-persistence, P = persistence, RR = relative risk, BP = blood pressure. Bold indicates significance at the $p < 0.05$ level.

Non-persistence use of antihypertensive therapy was significantly associated with an increased risk of recurrent PCI.

The cumulative decrease in antihypertensive persistence occurred more consistently than other cardiovascular medications. The median cumulative antihypertensive persistence of 50% occurred at 2.33 (95%CI = 1.90-2.75) years. Studies of antihypertensive persistence in ACS patients undergoing PCI have not been widely conducted. Most of them are conducted usually on antihypertensive users in general. A Swedish study in hypertensive patients showed a persistence rate of 57% at one year since starting therapy, and persistence continued to decline by 43% at two years since starting therapy (Qvarnström *et al.*, 2016), Lower than the persistence in this study. A German study showed antihypertensive persistence between 56-64% (depending on the type of antihypertensive) one year after starting therapy and decreased to 43-49% two years after therapy (Grimmsmann *et al.*, 2014). In Korea, antihypertensive persistence in one year since starting the therapy is slightly higher, at 62.07%, with an average duration of 276.5±123.1 days (Ah Y *et al.*, 2015). Another poor long-term persistence and adherence to antihypertensive were found among older Australians, which dropped to 21-42% by three years. The majority of discontinuations occurred within the 6- to 12-month period following initiation (Si S *et al.*, 2019). Low adherence to evidence-based therapies post-PCI, including dual antiplatelet therapy, beta-blockers, statin, and ACE inhibitor or ARB, was found in Qatar, with a rate of 28.4% over a one-year follow-up (Rahhal *et al.*, 2021). A study from Rotterdam, Netherlands, has identified the fact that only one-third of patients undergoing revascularization for complex coronary artery disease with either PCI or coronary artery bypass grafting (CABG) were receiving optimal medical therapy at the 5-year follow-up. Lack of Optimal Medical Therapy (OMT) was associated with adverse events, including death (Iqbal *et al.*, 2015). Interestingly, Reuter *et al.* (2015) described patients in their population with a history of heart failure (STEMI) who had high adherence to antihypertension such as beta-blockers, ACE-inhibitors or ARBs, and diuretics within three years of medication (Reuter *et al.*, 2015). A study from Thailand also reported medication adherence of antiplatelets, ACEIs/ARBs, beta-blockers, and statins among patients with ACS showed that after a median follow-up of 1.5 years, the overall

medication adherence was very high (more than 90% for each of the four classes of medicines) (Chinwong *et al.*, 2021).

Hypertension was associated with increased morbidity and mortality in patients after coronary artery disease. Saluveer *et al.* (2017) described that high blood pressure in patients after acute MI may accelerate and worsen the process of post-infarction cardiac remodeling. It was also associated with increased mortality risk in patients who were revascularized with PCI, with the total mortality at any time during the study period being 20.4% in hypertensive patients (Saluveer *et al*., 2017). This retrospective cohort study also showed an association between the non-persistence of antihypertensive use and increased incidence of MACE, MACCE, myocardial infarction, recurrent PCI, and hospitalization. However, the meaningful association was only seen in the MACCE outcome. This study is in line with a study by Corrao *et al*. (2017), which proved that continuous use of antihypertensive drugs would reduce the risk of cardiovascular events compared to patients who discontinue antihypertensive use (Corrao *et al.*, 2017). A Dutch study is also in line with this study, where the results show a link between the discontinuation of antihypertensive drugs with the incidence of acute myocardial infarction, and this association is significant, especially for beta-blockers drugs, calcium antagonists, and diuretics (Alharbi *et al.*, 2017). Patients at the Cardiology Department of Spedali Civili of Brescia, Italy, who were treated at discharge with at least 50% of the target dose of ACEi/ARBs and or beta-blockers showed an independent lower risk of all-cause death and heart failure (HF) rehospitalization (Carubelli *et al.*, 2021). Another study from China was similar, showing that medication adherence prevalence among Chinese myocardial infarction patients post-PCI therapy was suboptimal. Thus medication nonadherence is independently associated with MACE (Hou *et al.*, 2019).

Our study had described the association between non-persistence with antihypertensive with some clinical outcomes, but it was still in general of antihypertensive drugs. Angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB) are indicated as first-line treatment for heart failure, which could be a consequence of acute myocardial infarction (AMI). It is used to reduce mortality as well as rates of reinfarction and hospitalizations. A study by Febrinasari *et al.* (2019) concluded that ACEi-based therapy has similar efficacy as ARB-based treatment in terms of mortality and all causes of hospitalization. ARB is only recommended for ACEi-intolerant patients (Febrinasari *et al.*, 2019). Some other studies showed that full adherence to specific antihypertensive drugs, beta-blocker, had a statistically significantly lower risk of MACE.

In contrast, full adherence to other guideline-recommended medicines (antiplatelet drugs, ACEis/ARBs, and statins) did not significantly reduce the risk of MACE. However, it was still associated with a reduced one-year cardiovascular event risk (Chinwong *et al.*, 2021). Good adherence to beta-blocker therapy affects both coronary plaque and overall mortality positively. In contrast, poor adherence was associated with increased long-term mortality among ACS patients (Kawashiri *et al.*, 2017). Desta *et al.* (2021) showed that adherence to beta-blocker treatment was independently associated with a marked reduction of all-cause mortality and the combined endpoint of HF readmission and death in acute myocardial infarction patients. Beta-blockers therapy has been shown to improve survival after acute myocardial infarction (AMI) and reduce mortality and morbidity in patients with chronic heart failure (Si S *et al.*, 2019). The research conducted by Watanabe *et al.* (2018) contrasts with previous studies. They concluded that long-term carvedilol therapy added to contemporary evidence-based medications did not seem beneficial in selected STEMI patients treated with primary PCI (Maron *et al.*, 2011).

Factors that modify the relationship between non-persistence antihypertensive with MACE or MACCE are a long history of diabetes mellitus and diastolic blood pressure. Some studies showed that metabolic syndrome is meaningfully associated with the incidence of MACE in people with hypertension. Metabolic syndrome in this study was defined as a hypertensive condition accompanied by 1-2 conditions, namely abdominal obesity, hypertriglyceridemia, low HDL cholesterol, and impaired glucose metabolism. Thus, simultaneous reduction of LDL-cholesterol and blood pressure, at least within the guidelines-recommended levels, is important for the secondary prevention of coronary artery disease and significantly associated with substantial reductions in major cardiovascular events (Georgiopoulos *et al.*, 2016; Kawashiri *et al.*, 2017; Kanda *et al.*, 2021). Diabetes mellitus is one of the cardiovascular risk factors that also play a big role in cardiovascular events. It is shown in our study in Table 3 that several characteristics tend to increase

the adjusted relative risk (RR) value for MACE. Two factors that significantly increase the adjusted RR for MACE are the history of diabetes mellitus (RR 5.51, 95%CI = 1.52-19.97) and diastolic blood pressure ≥ 80 mmHg (RR 2.55, 95% CI = 0.35-3.61). A study has found a significant increase in long-term mortality from 8.21% in non-metabolic syndrome patients to 12.1% in metabolic syndrome patients. The association of diabetes mellitus and hypertension may lead to higher mortality in these patients after PCI (Maron *et al.*, 2011; Bundhun *et al.*, 2015). Kim *et al*. (2020) supported their studies in South Korea, where a group of myocardial infarction patients after stent implantation with both diabetes mellitus and hypertension showed the highest cumulative incidence of new-onset heart failure among other groups (diabetes mellitus alone, hypertension alone, and without both of them). This finding is in contrast to another study that has found that patients after PCI with both DM and hypertension had a significantly higher risk of developing the multi-vessel disease. However, patients with DM alone have higher mortality than those with both DM and hypertension. Comorbidity with DM in hypertension patients might have an additional risk of multi-vessel disease compared to patients with hypertension alone (Lin *et al*., 2017).

The present study has some limitations. First, the medical record data used in this study. There is the possibility of coding errors and incomplete information about patient characteristics that may be relevant to the study and may limit the generalizability of the results. Second, we use a sample from patients using antihypertensive drugs in general. At the same time, according to the guideline for acute coronary syndrome patients, there are many classes of antihypertensive drugs, such as ACE inhibitors, ARBs, diuretics, beta-blockers, and many others. Thus, we hope that future studies could differ in the association between each class of antihypertensive drugs with the clinical outcomes or cardiovascular events. Third, the dose of antihypertensive drugs has not been described. We know that optimal dose is one of the keys to successful therapy besides treatment persistence. The dose variety could bring different results associated with clinical outcomes.

CONCLUSION

In ACS patients after PCI, not all patients continue their drug exactly as prescribed. The cumulative persistence of antihypertensive drug use consistently decreased until the end of the fourth year after PCI, with a cumulative median persistence of 50% at 2.33 (95%CI = 1.90-2.75) years. In ACS patients undergoing PCI, there is a meaningful relationship between the non-persistence of antihypertensive with MACCE incidence (RR 1.94, 95%CI = 1.02-3.71) and recurrent PCI (RR 2.68, 95%CI = 1.03-6.99). A history of diabetes mellitus and diastolic blood pressure modifies the associations between the non-persistence of antihypertensive with MACCE incidence. Although there are some limitations, this study provides real-world evidence that helps discover the association between persistence to antihypertensive therapy and clinical outcomes that can promote secondary prevention for ACS patients after PCI.

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