

High Apo B/Apo A-1 Serum Ratio As A Predictor of in-Hospital Major Adverse Cardiovascular Events in Acute Coronary Syndrome Patients

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Abstract

Background. An increased level of apo B and decreased level of apo A-1 are thought to be better predictors of myocardial infarction than conventional lipid parameters in healthy individuals and/or have coronary artery disease risk factors. Literatures said that HDL, LDL and apolipoprotein may have a role in haemostatic and thrombotic process. The present study aimed to investigate whether apo B/ apo A-1 ratio has a predictive role in hospitalised ACS patients to develop major adverse cardiac events (MACE).

Methods. We performed a prospective cohort study and examined 182 ACS patients hospitalised in dr. Sardjito General Hospital Yogyakarta consecutively since September 2013, and evaluated ischaemia heart disease risk factors, measured concentration of apo B/apo A-1 ratio and conventional lipid parameters from plasma, and finally assessed the in-hospital MACE outcome. Apo B/Apo A-1 ratio cut off point in this study was taken from ROC curve analysis. Relation between in-hospital MACE with level of apo B/apo A-1 ratio was analysed using SPSS.

Results. From 182 ACS subjects, 51 patients had MACE (MACE group) and 131 patients didn't develop MACE (non-MACE group). From ROC curve, we set cut off point for apo B/apo A-1 ratio was 0,865. Subjects with an apo B/apo A-1 ratio $\geq 0,865$ had a significantly increased risk to suffer a cardiovascular event (MACE) during in-hospital follow-up. In a multiple logistic regression model, elevated apo B/apo A-1 ratio was an independent predictor for MACE during in-hospital follow-up (OR 3,17; 95%CI 1,299 - 7,738; $p = 0,011$).

Conclusion. The results showed that the elevated apo B/apo A-1 ratio $\geq 0,865$ was an independent predictor of MACE, with three-folds increase of risk compared to group of apo B/apo A-1 ratio < 0.865 , during in-hospital follow-up in ACS patients.

Keywords: apolipoprotein B; apolipoprotein A-1; apolipoprotein ratio; acute coronary syndrome; major adverse cardiovascular events

Background

Acute coronary syndrome (ACS) is an event which is marked by changes in coronary circulation, generally in the form of a reduction or cessation of blood flow in the coronary arteries, which is generally caused by the formation of a blood clot on the ruptured atherosclerotic plaque. A good indicator is required for risk assessment of major cardiovascular events (MACE).¹

Lipid profile and lipoprotein particles determines the ability of plasma lipids in the formation of atherosclerotic plaque. Among the risk factors that have been identified as a risk factor for coronary heart disease, some constituent components of the lipid and lipoprotein known as a mediator are considered as coronary heart disease markers. The lipid components here particularly are higher plasma total cholesterol, high LDL cholesterol (low density lipoprotein) cholesterol,

high triglycerides, high apolipoprotein B (apo B), low HDL (high density lipoprotein) and low apolipoprotein A-1 (Apo A-1).^{2,3} Among patients who have recently experienced ACS, intensive statin therapy provides protection against death and MACE compared to standard therapy.^{4,5}

Currently, studies that reveal apolipoprotein as a better MACE predictor than the conventional lipid parameter are frequently found. Apolipoprotein B (apo B) is a protein found on the surface of LDL, VLDL (very low density lipoprotein) and chylomicrons. Apolipoprotein A-1 (Apo A-1) found on the surface of the HDL particle. Some of these studies said the value of apo B/apo A-1 ratio is an excellent tool for assessing cardiovascular risk. This ratio reflects the relationship between the pro-atherogenic effects of apo B-containing lipoproteins and anti-atherogenic fraction of HDL. The higher the apo B/apo A-1 ratio group,

the higher the risk MACE, namely the risk of myocardial infarction and other cardiovascular manifestations.^{6,7} Some studies suggest that HDL lipoprotein and its carrier which is apolipoprotein A-1, not only it has a "reverse cholesterol transport, but also has antioxidant effects, anti-inflammatory, antithrombotic on vascular endothelial cells. Moreover, it is also able to prevent further vascular endothelial dysfunction, plaque rupture, thrombosis arterial and also inhibit the atherosclerosis and restenosis process.⁸

In regards of method, there are some advantages in measurement of apolipoprotein over conventional lipid measurement parameter. In standard LDL measurement, Friedwald formula determined by triglycerides levels requires fasting before blood sampling. Based on a meta-analysis of ERFC (Emerging Risk Factor Collaboration) in 2009, the measurement of lipid ratio and the ratio of apolipoprotein can be performed without fasting prior to the blood sampling.^{9,10}

Previous research has shown some atherogenic lipid plasma are independent predictors of coronary heart disease, yet research data indicates the involvement of specific atherogenic lipid plasma in ACS is still very limited. These studies examine subjects that have not experienced or have a history of ACS before, therefore it reflects more or less about chronic effect of the apo B/apo A-1 ratio group as a predictor of MACE. Moss *et al.* (1999) examined ACS patients and followed up to two months later, and concluded that abnormalities in lipid transport, which characterised by low apo A-1 and high apo B are independently contribute to the incidence of recurrent coronary events.¹¹ Until now, there is not any study examining the relationship between apo B/apo A-1 ratio group and occurrence of MACE in ACS patients, especially during hospitalisation.

Methods

Subjects

The design of this study was a prospective cohort study. The aim was to evaluate the relationship between apo B/apo A-1 ratio and the occurrence of MACE in ACS patients during hospitalisation at Dr. Sardjito General Hospital Yogyakarta from September 2013 until January 2014. Male and female patients who were 30-85 years of age and had been admitted to coronary care unit with a diagnosis of ACS, and agreed

to participate in this study were eligible for enrolment. Subjects were taken consecutively (non-probability sampling) until the minimum sample size was achieved. Patients were excluded from enrolment if they had an end stage chronic kidney disease, chronic heart failure; patients with comorbid of sepsis, deep vein thrombosis, acute limb ischemia, hepatic cirrhosis, malignancy; pregnancy. The subjects were treated at the discretion of their attending cardiologists. The therapy and medication received at the time of baseline enrolment and during hospitalisation were recorded.

The demographic characteristics (age, gender, body mass index/BMI), risk factors for ischemic heart disease (smoking history, history of hypertension, diabetes mellitus, previous cardiovascular disease and lipid disorders), clinical spectrum of ACS, as well as the conventional lipid parameters (total cholesterol, HDL, LDL, triglyceride), and ratio apo B/apo A-1 of the enrolled patients were measured within the first 24 hours of admission. Other baseline clinical data were recorded, i.e. systolic and diastolic blood pressure, routine blood tests: hemoglobin, leukocyte numbers and numbers of platelets, creatinine, glucose, and cardiac enzyme tests (CKMB and troponin I). Subsequently, the subjects were followed up until discharge from hospital.

The clinical spectrum of ACS were based on symptoms of chest pain of angina, electrocardiographic abnormalities and cardiac enzyme levels in accordance with the criteria ACCF/AHA (2013). The clinical spectrum included ST-segment elevation acute myocardial infarction (STEMI), non-ST segment elevation acute myocardial infarction (NSTEMI) and unstable angina pectoris (UAP). This study was approved by the Medical and Health Research Ethics Committee at our institution.

Apolipoprotein measurement

As much as 3 cc of blood samples taken with a phlebotomy technique when the patient (fasting or non-fasting state) entered the hospital, then the blood sample was put in a tube containing clot activator. Next, the sample is then centrifuged at 2000 rpm for 10 minutes in order to obtain the serum to be stored in a -80 °C freezer. Serum samples were collected until the sample size is met, then will be investigated apo B and apo A-1

below the apo B/apo A-1 ratio group simultaneously using automated tools immunoturbidimetric method (Hitachi 902) and reagent Daiichi (Sekisui Medical, Japan). Analyses were performed according to the manufacturers' specifications, and quality control was within the recommended precision for each test.

Study Endpoints

The pre-specified end points were MACE during hospitalisation including death of any cardiovascular causes, reinfarction, cardiogenic shock, acute heart failure, ventricular tachycardia or ventricular fibrillation (VT/VF) that require cardioversion or defibrillation, prolonged angina, acute stroke, as well as the conditions that indicate the need for early coronary intervention. Diagnosis of these condition was verified by attending cardiologists.

The independent variable in this study is the apo B/apo A-1 ratio obtained from the serum of patients taken at hospital admission. Dependent variable in this study was the occurrence of MACE during hospitalisation. While confounding variables include the clinical spectrum of acute coronary syndromes, age, gender, body mass index (BMI), hypertension, diabetes mellitus (DM), dyslipidemia, smoking history, family history of heart disease, cardiac enzymes (CKMB, troponin I), as well as the management of SKA in patients during hospitalisation.

Statistical analysis

Subjects were divided into two groups: the group who developed MACE and group without MACE (non-MACE). Continuous data between groups were compared by unpaired t test. Categorical data between groups were compared with chi-square test. In the 2x2 tables, Fisher exact test was used when Chi-Square test requirements are not met. Bivariate analysis was conducted to analyze whether the apo B/apo A-1 ratio group as a predictor of MACE. For this analysis we categorised the value of apo B/apo A-1 ratio into 2 categories, high and low apo B/apo A-1 ratio group. We determined the cut off point using ROC curve analysis. Multivariate analyses were performed to see whether the apo B/apo A-1 ratio group as an independent predictor of MACE. Analysis considered significant when the p value <0.05. Data analysis was performed with SPSS version 22.

Results

In total, 182 patients met the inclusion criteria and thus enrolled in this study. The clinical characteristics of the entire study population as well as those with and without coronary events during follow-up are presented in Table 1.

Clinical characteristic of patients in MACE group and control are shown in table 1. There are no significant difference in demographic characteristics, previous history of hypertension, diabetes, dyslipidemia, and coronary artery disease, as well as clinical spectrum of ACS between the two groups.

From 182 ACS patients, 51 (28%) patients had cardiovascular events (MACE group) and 131 (72%) patients did not experience MACE (non-MACE group). In MACE group, there were 11 (6%) patients died, 8 (4.4%) incidents of reinfarction, 26 (14.3%) patients had Killip II-IV, 2 (1.1%) patients had prolonged angina, 11 (6%) patients had VT / VF requiring cardioversion or defibrillation and/or intravenous anti-arrhythmic drugs, 7 (3.8%) patients had to be done PCI immediately, and 3 (1.6%) patients experienced acute stroke. Patients in MACE group showed significant increase of CKMB and creatinine value compared to non-MACE group. The use of beta-blockers were lower in the MACE group, and the invasive (PCI) procedure were higher in the MACE group compared to non-MACE group ($p < 0.05$) (Table 1).

In this study, we need a cut-off point value to classify the apo B/apo A-1 ratio value. In our knowledge, there had been no previous studies that can be used as a reference value of the cut-off point. So we determined the value With SPSS, after entering the value of the apo B/apo A-1 ratio group into a ROC analysis, we obtained a graph as in figure 1. Determination of clinical cut-off point was defined by the researchers as expected and according to study purposes, from the point of intersection in ROC (Receiver Operating Characteristic) curve analysis. Based on research by Walldius *et al.* (2001), the value of > 0.9 is a high risk of myocardial infarction¹², and in this present study that value had a sensitivity of 47-56%, and a specificity of 51-55%. However, the value of 0.865 had higher sensitivity at 71% and specificity 53%, therefore we determined this value to be the optimal cut-off point for apo B/apo A-1 ratio in this study. Thus, the patients were divided into two groups according to apo B/apo A-1 ratio,

Table 1. Baseline characteristics of the subjects based on outcomes (MACE)

Variable	Total (n=182)	MACE group (n=51)	Non-MACE group (n=131)	P value
Age (years), mean \pm SD	60.42 \pm 10.3	61.0 \pm 9.9	60.0 \pm 10.5	0.541
Male/female, n	134/48	36/15	98/33	0.578
BMI (kg/m ²), median (span)	23.4 (15.1 – 35.1)	23.6 (16.8 - 35.1)	23.4 (15.1-34.2)	0.145
Previous history				
Diabetes mellitus, n(%)	58 (31)	21 (41)	37 (29)	0.181
Hypertension, n(%)	124 (68)	38 (74)	85 (64)	0.868
Previous CVD, n(%)	52 (28)	12 (23)	40 (30)	0.347
Smoking, n(%)	105 (57)	22 (43)	83 (63)	0.013
Family history of CVD, n(%)	4 (2)	2 (4)	2 (2)	0.589
Dyslipidemia, n(%)	53 (29)	15 (29)	38 (33)	0.694
ACS clinical spectrum, n(%)				
STEMI	106 (58)	35 (68.6)	71 (54.2)	0.137
NSTEMI	39 (21)	10 (19.6)	29 (22.1)	
UAP	37 (20)	6 (11.8)	31 (23.7)	
Lab. examination				
CKMB, median (span)	46 (3 - 735)	105 (12-735)	41 (3-706)	0.000
Creatinin (mg/dL), mean \pm SD	1.26 \pm 0.68	1.4 \pm 0.95	1.1 \pm 0.52	0.029
Lipid Parameter, mean \pm SD				
Total cholesterol, (mg/dL)	184 \pm 45.8	188.8 \pm 42.85	179.88 \pm 53.26	0.294
Triglycerid, (mg/dL)	123 \pm 66.8	136.94 \pm 90.06	119.05 \pm 54.44	0.120
HDL, (mg/dL)	42 (17 - 189)	40 (17 - 144)	42 (19 - 189)	0.400
LDL, (mg/dL)	117 \pm 45.6	119.76 \pm 46.9	115.88 \pm 45.03	0.501
Apolipoprotein A-1 (g/dL)	102 (28 - 184)	96 (36-145)	104 (28-184)	0.043
Apolipoprotein B (g/dL)	92 \pm 31.3	89 \pm 33.4	93 \pm 30.0	0.467
In-hospital medication and therapy				
Heparin, n(%)	163 (89)	43 (26.4)	120 (73.6)	0.149
Beta blocker, n(%)	144 (79)	35 (68)	109 (83)	0.030
Statin, n(%)	160 (87)	46 (93)	114 (98.3)	0.156
Thrombolysis, n(%)	26 (14)	11 (22)	15 (12.9)	0.140
Primary PCI, n(%)	53 (29)	23 (46)	30 (25.9)	0.008

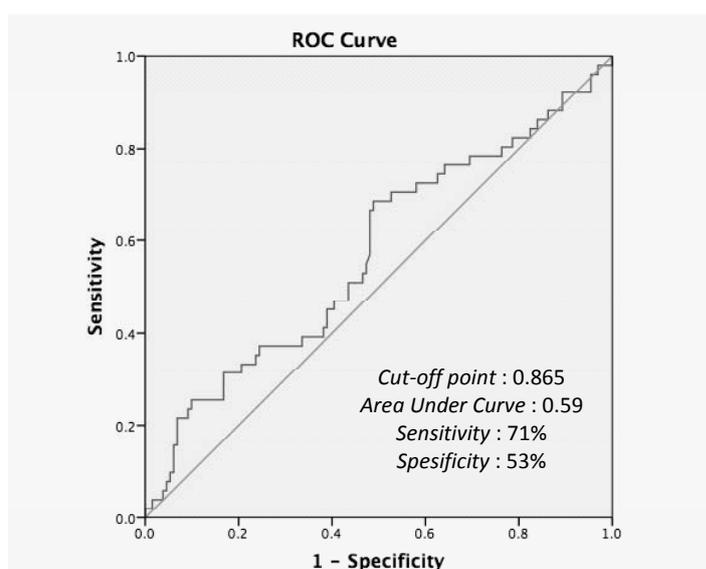


Figure 1. Receiver-operating characteristics (ROC) curve analysis: determining cut-off point of Apo B/ apo A-1 ratio value based on the incidence of MACE in ACS subjects

Table 2. Association between apo B/apo A-1 ratio and MACE during hospitalization in SKA subjects

Variable	End point				RR	95% CI	P value
	MACE		non-MACE				
	n	%	n	%			
High Apo B/ apo A-1 ratio ($\geq 0,865$) n = 105	36	34	69	66	1.76	1.040 - 2.97	0.028
Low Apo B/ apo A-1 ratio ($< 0,865$) n = 77	15	19	62	80			
Total	51	28	131	71			

Table 3. Multivariate logistic regression risk analysis of clinical variables to occurrence of in-hospital MACE

Variables	OR	95% CI	P value
STEMI	0.874	0.322 - 2.378	0.793
Beta blocker	0.751	0.231 - 2.439	0.634
Trombolysis	1.488	0.351 - 6.302	0.589
Heparinization	0.496	0.119 - 2.077	0.337
Statin	3.024	0.338 - 27.038	0.322
Creatinin	1.410	0.779 - 2.552	0.256
PCI	0.522	0.217 - 1.258	0.147
Triglyceride	1.005	0.999 - 1.010	0.109
High Apo B/ apo A-1 ratio ($\geq 0,865$)	3.171	1.299 - 7.738	0.011*
Smoker	0.275	0.114 - 0.666	0.004*
CKMB	1.008	1.004 - 1.012	0.000*

Remarks: * = statistically significant ($p < 0.05$).

Table 4. Sub analysis of the relationship between the high apo B/apo A-1 ratio with each type of MACE

MACE	High Apo Ratio n (%)	Low Apo Ratio n (%)	RR	CI 95%	p
Death	6 (5.7)	5 (6.5)	0.88	0.279 - 2.779	0.827
Reinfarction	5 (4.8)	3 (3.9)	1.22	0.301 - 4.960	1.000
Kiliip II-IV	18 (17)	8 (10.4)	1.65	0.757 - 3.596	0.198
Prolonged angina	2 (1.9)	0	#	#	#
VT/VF	6 (5.7)	5 (6.5)	0.88	0.279 - 2.779	1.000
Early PCI	6 (5.7)	1 (1.3)	4.40	0.541 - 35.805	0.241
Acute stroke	3 (2.9)	0	#	#	#

Description: RR = relative risk; # = Can not be assessed

where the value ≥ 0.865 belong to the high apo B/ apo A-1 ratio group; and value < 0.865 as low apo B/apo A-1 ratio group.

Table 2 shows that the proportion of subjects with MACE in the group with a high apo B/apo A-1 was higher than the low apo B/apo A-1 ratio group. This difference was statistically significant (34% vs. 19%; $p = 0.028$). Patients with the high apo B/ apo A-1 ratio had 1.76 times higher possibility to develop MACE compared with patients with the low apo B/apo A-1 ratio group.

A multivariate logistic regression model was constructed to determine the independent contribution that apolipoprotein ratio made to occurrence of MACE in the presence of relevant clinical variables. Eleven clinical variables entered the clinical model at $P < 0.25$ (table 2). Only apo B/apo A-1 ratio, smoker, and CKMB entered the clinical model at $P < 0.05$, with odds ratio 3.171, 0.275, and 1.008, respectively (table 3).

We then conducted sub analysis to assess the relationship between the high apo B/apo A-1

ratio (≥ 0.865) with the incidence of each type of MACE studied (Table 4).

Patients in the high apo B/apo A-1 ratio group had a higher proportion of subjects who developed deaths (due to any cause), the incidence of reinfarction, Killip II-IV, prolonged angina, condition requiring early PCI, and the incidence of acute stroke than the low Apo B/apo A-1 ratio group, but the difference in this proportion was not statistically significant.

Discussion

Age, hypertension, smoking and dyslipidemia are the most common cardiovascular risk factors found in developing countries.¹³ Baseline characteristics of the subjects in this study is dominated by subjects with risk factors for old age (mean 60 years), male gender, smoking, hypertension and dyslipidaemia, but there was no statistically significant difference between the MACE and non-MACE group. Statistically, the basic characteristics of the two groups did not differ significantly in terms of demographics, disease history and previous CHD risk factors, ACS clinical spectrum, as well as standard lipid parameters. These indicate that the general characteristics of study subjects did not affect the results.

In the ULSAM study (2004) mentioned an increase in the apo B/apo A-1 ratio value in line with an increased risk of myocardial infarction, and the ratio of 0.87-1.23 increases the incidence of myocardial infarction up to 30%.¹⁴ Thus, the cut off point of 0.865 in this study include in moderate to high risk category for the occurrence of cardiovascular events according to previous studies. The analysis of this study showed that in ACS patients who have apo B/apo A-1 ratio ≥ 0.865 have 1.76 times greater risk of experiencing MACE compared with patients with a apo B/apo A-1 ratio < 0.865 during hospitalisation. Once included in the multivariate analysis with logistic regression OR of MACE increased to 3.171, so it is evident that this apolipoprotein ratio is independent predictor factors to the occurrence of MACE during hospitalisation in ACS population. This is in line with study results by Moss et al. (1999) which states that low apo A-1 and high apo B can identify patients who experienced recurrent cardiovascular events in two months after an ACS.¹¹

Apolipoprotein directly involved in the mobilization of lipids and the metabolic conversion

of the various classes of lipoproteins in circulation. Apolipoprotein synthesis influenced by genetic control, but can also be influenced by diet, hormonal, and medical treatment. Apo A-1 is found in the HDL and plays an important role in the process of reverse cholesterol transport (RCT). In addition, apo A-1 has a cofactor activity of the enzyme LCAT, which serves cholesterol esterifying hence it is more efficient when transported to the liver. Besides, apo A-1 is a cholesterol scavenger (cleaners) in circulation. Whereas apo B is contained in lipoproteins which is known to be atherogenic, i.e LDL, VLDL and sdLDL, so the number of Apo B in all atherogenic particles likely to be a better risk factor than total cholesterol and LDL.

As described previously, apolipoprotein might have a role in hemostasis and thrombosis. Lipoprotein and apolipoprotein abnormalities, especially LDL (apoB-containing) can cause endothelial dysfunction by interfering with the balance related vasodilation function NO, prostacyclin and thromboxane A₂. In contrast, HDL, inversely correlated with platelet-thrombus formation. Low HDL (lower apoA-1 levels) can increase activity of PAF and initiated thrombus formation.^{8,15} Study by Moss et al. (1999) mentions that low apoA-1 and high apoB independently contribute to recurrent coronary events in ACS patients.¹¹ Intravascular thrombogenesis process might enhance in patients with ACS due to abnormalities in lipoprotein and apolipoprotein and will further increase the incidence of in-hospital MACE.

Several other variables were also an independent predictor to the occurrence of in-hospital MACE in ACS patients is CKMB levels and a history of smoking. Smith et al. (1976) states that high levels of CKMB is correlated with an extensive area of myocardial infarction, and hence worsen ventricular dysfunction, and then the risk of in-hospital MACE.¹⁵ In this study showed the proportion of smokers in the group MACE lower (43%) than in the group of non-MACE (63%). And this difference is statistically significant at the bivariate and multivariate analysis ($p < 0.05$). But in this study, data collection regarding smoking history was obtained from the anamneses, and thus there is possibility of passive smokers subjects included in the group of non-smokers, which may further affect the results of this study. According to a study by He et al. (1999) mentions that passive smokers have an increased risk of cardiovascular events.¹⁶ Therefore, this study

results in respect to smoker as a protective factors is still need further investigation.

In MACE group the proportion of beta-blockers therapy was lower than in non-MACE group (68% vs. 83%), and the difference was statistically significant proportions. One meta-analysis by Bangalore *et al.* (2014) states that beta-blocker does not have the effect of reduce mortality, but it can reduce the incidence of recurrent myocardial infarction and angina (in short-term).¹⁷ In relation to this study, the lower use of beta blockers at MACE group may affect the outcome of this study.

In MACE group, the proportion of revascularisation procedure with PCI was significantly higher than non-MACE group. The study by Wu *et al.* (2011) described that the primary PCI in STEMI population with the results of TIMI flow grade (TFG) 0/1 significantly associated with mortality and the incidence of MACE during hospitalisation.¹⁸ In this study, TFG was not assessed after PCI, so the estimation of successful by TFG measurement cannot be done objectively. In addition, in our study center, PCI procedure has not been done uniformly since it is relatively expensive, and constrained by financing and health insurance policy.

Our study showed that the lower use of statins during hospitalisation can increase the risk of MACE of 3 times, but this increase was not statistically significant. This is consistent with previous studies by Maruyama *et al.* (2011) which stated that the use of statins (pravastatin, atorvastatin or Pitavastatin) significantly prevent the occurrence MACE compared with no statin therapy in post-PCI patients in Japan.¹⁹ This results indicates that changes in lipid levels from baseline (decreased LDL and increased HDL) is important in the secondary prevention of MACE.

Study by Sniderman *et al.* (2007) mentioned that in the AMORIS subject population, the risk of fatal myocardial infarction increased in line with an increasing in the value of apo B/apo A-1 ratio.²⁰ The results of our study suggested that subjects with apo B/apo A-1 ratio ≥ 0.865 , significantly increasing the occurrence of MACE during hospitalisation. In table 4, in the high apo B/apo A-1 ratio group (≥ 0.865), early PCI procedure increased by 4.4 times, the incidence of reinfarction by 1.22 times and Killip \geq II condition by 1.65 times compared to the low Apo B/apo A-1 ratio group (< 0.865), but this increase was statistically not significant ($p > 0.05$). APSIS (Angina Prognosis Study In Stockholm) study stated that low apo A-1 and high apo B ratio is an independent

predictor of revascularisation done in stable angina pectoris populations.²² Study Moss *et al.* (1999) states that the value of high apo B and apo A-1 low is a statistically significant predictor of the incidence of reinfarction in ACS population.¹¹ In our study, this results is not significant statistically, probably due to lack of power for this subanalysis.

Study Limitations

This study did not analyse the type and dose of statins used, where it is known that administration of statins in different preparations with different dosages, will yield a different therapy intensity and response. Furthermore, in this study, we did not adjust the MACE outcomes with any other valid prognostic score that already exist such as GRACE or TIMI risk score. Dyslipidemia therapy target based on this parameters can be considered and might also help to predict in-hospital major cardiovascular events, especially in ACS patients. Further research is needed on the effect of the apo B/apo A-1 ratio on MACE, adjusted to valid prognostic scores such as GRACE and TIMI risk score.

Conclusions

High apo B/apo A-1 ratio (≥ 0.865) is an independent predictor of MACE, with an increased risk of 3-fold compared to low apo B/apo A-1 ratio group (< 0.865) in patients with ACS.

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