Correlation between Small Dense Low Density Lipoprotein Level with Major Adverse Cardiac Event in Acute Coronary Syndrome Patients

Maria Debby Maharatno, Hariadi Hariawan, Budi Yuli Setianto

Department of Cardiology and Vascular Medicine
Faculty of Medicine Universitas Gadjah Mada - Dr. Sardjito General Hospital, Yogyakarta, Indonesia

Abstract

Background: Cardiovascular disease is one of major problems in developed and developing countries. Atherosclerosis process begins with endothelial dysfunction. Lipoprotein is important factor in atherogenesis. Previous study stated that about 50% of cardiovascular events happened in individuals with normal or low LDL, therefore LDL plasma level alone is not enough to identify individuals with major adverse cardiac events. Individuals with small dense LDL predominant have 3 times fold to have cardiovascular risk. The goal of this study is to know whether the level of sdLDL has impact on in hospital major adverse cardiac events (MACE) of acute coronary syndrome patients.

Methods: This was a cross sectional study, enrolling patients with acute coronary syndrome admitted and hospitalized in ICCU of Dr.Sardjito Hospital since September of 2013 until June 2015. The small dense LDL (sdLDLD) level was measured with previous formula using routine blood lipid component. Major adverse cardiac events (MACE) were determined upon observation during horpitalisation and defined as death, reinfarction, cardiogenic shock, acute heart failure, ventricular tachycardia or ventricular fibrillation, prolonged angina pain, and the need for immediate coronary intervention.

Results: There were 159 patients with mean age 60.80 ± 9.8 years involved in this study. One hundred eighteen (118) or 73% of patients were male. The mean of sdLDL level in patients with MACE was 108.34 ± 37.94 g/dl and mean sdLDL level in patients without MACE was 105.54 ± 43.10 g/dl. The level of sdLDL in patients without MACE was lower than patients with MACE (p=0.705). In this study we found the cut- off sdLDL level is ≥ 108.085 for higher sdLDL level and < 108.085 for lower sdLDL level. The higher sdLDL level have the prevalence ratio of 1.25 to develop MACE, however the value was not statistically significant.

Conclusion: The sdLDL level did not correlate with MACE in hospitalised patients with acute coronary syndrome.

Keywords: small dense LDL, acute coronary syndrome, MACE

Introduction

Cardiovascular disease is one of the major health problems in developed and developing countries. The disease is becoming the number one cause of death in the world each year. More than 3 million of these deaths occur before the age of 60 years. Deaths caused by heart disease of blood vessels, especially coronary heart disease and stroke is expected to continue to increase to 23.3 million deaths in 2030.[1]

In Indonesia, cardiovascular disease is on the increase and will provide loads of morbidity, disability and socio-economic burden for families of patients, communities, and countries. The prevalence of heart failure disease in Indonesia in 2013 is based on the doctor's diagnosis at 0:13%.[1] Coronary heart disease(CHD) is a disease that is caused by narrowing of the lumen of the coronary arteries due to atherosclerosis of the coronary artery wall, causing decreased blood flow and oxygen supply to the myocardium disorders.[2,3,4] In the course of the disease, CHD can be progressive and often changes suddenly from a stable condition into an acute state known as acute coronary syndrome (ACS). This syndrome consists of unstable angina pectoris, Non ST-Segment elevation myocardial infarction (NSTEMI), and ST segment elevation myocardial infarction (STEMI).

The process of atherosclerosis begins with endothelial dysfunction. Endothelial function is to maintain the balance between vasodilation and vasoconstriction, inhibition and stimulation, proliferation and migration of smooth muscle

cells, as well as between thrombogenesis and fibrinolysis. Inflammation plays a role in endothelial dysfunction.[5] One of the advances in medicine that is quite important is the identification of major risk factors for cardiovascular disease events. Lipoprotein plays an important role in atherogenesis. Low Density Lipoproteins-cholesterol (LDL-C) is the main target in CHD prevention guidelines. Plasma levels of LDL-C alone is not enough to identify an individual with cardiovascular events, because on average 50% of cardiovascular events occur in individuals with normal LDL levels even lower.[6]

Low density lipoprotein is composed of heterogeneous particles that differ in terms of density, size and chemical composition. Individuals with a predominance of small dense LDL (sdLDL) had a 3-fold increased risk of cardiovascular disease.[7] Currently, sdLDL has been underlined as new markers of potential cardiovascular disease risk in Western populations and Japan, which have high levels of LDL-C is relatively low.[7] In patients with ACS, high levels of sdLDL have more major cardiovascular events because macrophages containing much sdLDL had higher chemotactic activity and higher proteolitic so that conditions make the plaque become more unstable.[8]

Major adverse cardiovascular events (MACE) during hospitalization remains a problem encountered in the management of patients with ACS. Several risk factors have been identified as factors related to adverse events during hospitalization. Small dense low-density lipoprotein has been identified as a risk factor for coronary artery disease, whether it can be used to assess the MACE during hospitalization in acute coronary syndrome is still not fully known, moreover sdLDL research on the acute phase of the ACS is still very limited.

The aim of this study is to investigate whether high levels of sdLDL have a relationship with MACE during hospitalization in patients with ACS. The author's knowledge there has been no research on the relationship between the sdLDL levels after acute coronary syndrome with MACE, especially during hospitalization.

Methods

This study was an observational study. The study design was cross-sectional study, which assessed the relationship between levels of sdLDL during hospitalisation with the outcomes of major adverse cardiovascular events (MACE). The study started from September 2013 until minimal sample size requirement completed.

The subjects were patients with ACS and hospitalized in the ICCU of Dr. Sardjito General Hospital Yogyakarta, Indonesia using sequential / consecutive enrolling methods. The inclusion criteria for this study were: patients with ACS who were diagnosed according to the criteria of the guidelines of the American College of Cardiology Foundation (ACCF) / American Heart Association (AHA) 2013, patients aged 30-80 years, and agreed to participate in the study. The exclusion criteria were patients with a history: Stage V chronic renal failure, chronic heart failure, and liver cirrhosis, patients with comorbidities: acute stroke, acute infections, sepsis and venous or arterial thromboembolism and patients with malignancy. Subjects were observed during intensive hospitalisation in ICCU. The MACE consisted of death, reinfarction, cardiogenic shock, acute heart failure, ventricular tachycardia or ventricular fibrillation (VT / VF), prolonged angina pain, as well as the conditions that indicate the need for immediate coronary intervention.

The independent variable was the level of sdLDL and dependent variable of this study was MACE during hospitalisation in ICCU. An sdLDL level was calculated by the formula[9] : sdLDL = 0.94 total cholesterol – 0.94 HDL – 0.19 TG/ Apo-B – 0.09 chol + 0.09 HDL – 0.08 TG. HDL was high density lipoprotein, TG was triglyceride and Apo-B was apolipoprotein B. The unit value was set in mg/dL.

The statistical analysis was performed by using the chi-square test. Data analysis was performed with SPSS version 22 package. The research was conducted after achieving an approval from the Ethics Committee of Research, Faculty of Medicine, Universitas Gadjah Mada.

Result

The number of subjects in this the study was 159 patients and composed of 73.8% male, 25.6% female with mean age of 60.8 years. The characteristics of the study subjects was shown in table 1.

The acute coronary syndrome classification was STEMI (61%), NSTEMI (18.2%) and unstable angina (20.8%). The proportion of subjects with

Table 1. Baseline characteristics

Variable	Value (n= 159)
Age (years), mean ± SD	60.80 ± 9.8
Male/ Female, (%)	118/41 (73.8/25.6)
History, n (%)	
Diabetes Mellitus	50 (31.4)
Hypertension	118 (74.2)
CHD previous	46 (28.9)
Smoking	
• Smokers	90 (56.6)
• Non-smokers	69 (43.4)
Family history of CHD	4 (2.5)
Dyslipidemia	48 (30.2)
The clinical spectrum of ACS, n(%)	97 (61)
• STEMI	29 (18.2)
• NSTEMI	33 (20.8)
• UAP	
CKMB, mean ± SD	101.063 ± 130.4
Creatinine (mg/dL), mean ± SD	1.236 ± 0.708
Lipid parameters, mean ± SD	
Cholesterol total (mg/dL)	184.188 ± 47.219
Triglycerides (mg/dL)	123.626 ± 68.116
HDL (mg/dL)	47.117 ± 23.554
LDL (mg/dL)	117 ± 45.44
Treatment in hospital; n (%)	
Heparin	142 (89.3)
Beta blockers	120 (75.5)
Statin	154 (96.9)
Thrombolysis	26 (16.1)
PCI	52 (32.7)

SD: Standard Deviations, CHD: Coronary Heart Disease, STEMI: ST-segment elevation myocardial infarct, NSTEMI: non ST segment elevation myocardial infarct, UAP: Unstable Angina pectoris, CKMB: Creatine Kinase isoenzyme MB, HDL: High Density Lipoprotein, LDL: Low Density Lipoprotein, sdLDL: small dense low-density lipoprotein, PCI: Percutaneous Coronary Intervention, ACS: Acute Coronary Syndrome

risk factors for diabetes mellitus was 50 patients (31.4%), hypertension 118 (74.2%), smokers 90 patients (56.6%), CHD history of 46 patients (28.9%), history CHD in a family of 4 patients (2.5%) and dyslipidemia 48 (30.2%).

Among 159 subjects, 44 patients have MACE (MACE group) and 115 patients did not experience MACE (group without MACE). In the group of MACE there were 10 (22.7%) patients died, 3 (6.8%) reinfarction, 16 (36.4%) patients had Killip II-IV (acute heart failure), 4 (7.2%) patients had ventricular tachycardia/ventricular fibrillation requiring defibrillation or intravenous antiarrhythmic drugs, 52 (32.7%) patients had to be done PCI immediately because of medical indications, and 1 (2.3%) patient experienced acute stroke during hospitalization.

Statistically, the characteristics of the two groups there was no significant difference in terms of demographics, disease history, previous CHD risk factors, clinical spectrum of ACS and a standard lipid parameters. The mean CKMB and creatinine were higher in the MACE group compared to the group without MACE, while the average use of beta blockers in the MACE group was lower than the group without MACE ($p < 0.05$) (table 2).

This was consistent with the theory that high levels of cardiac enzymes such as CKMB or troponin I, the MACE was higher as compared to those with normal cardiac enzyme levels. The higher the levels, the worst prognosis and increased MACE. This was because that the higher cardiac enzymes were detected in laboratory indicate extensive damaged of heart muscle.[10] Cardiovascular events was higher in patients with chronic kidney disease (CKD), and will increase the incidence of cardiovascular 10-30 times higher than patients who did not suffer from CKD.[11]

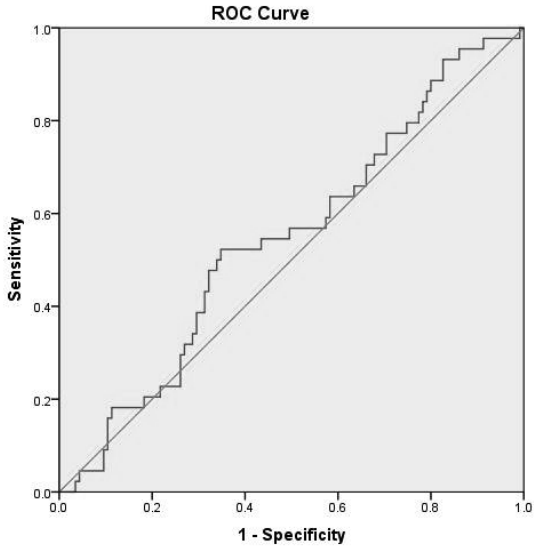

Figure 1. Receiver-operating characteristics curve (ROC) of sdLDL level value based on MACE during hospitalization in subjects with ACS

Levels of LDL in the non MACE and MACE groups were higher than the normal reference value, indicating a high risk for developing CHD. The sdLDL levels was 108.34 ± 37.94 mg/dL in the MACE group and 105.54 ± 45.97 mg/dL in the non MACE group. The sdLDL level at MACE group was higher than the non MACE group but there was no statistically significant difference between two groups ($p = 0.705$). In this study, we need a cut-off point value to determine sdLDL level in patients

Tabel 2. Analysis between groups MACE and non MACE

	MACE (n= 44)	non MACE (n= 115)	*p*
Age (years), mean ±	61.02 ± 11.08	60.72 ± 9.39	0.863
male/female	32/12	86/29	0.791
History, n(%)			
Diabetes Mellitus	15 (34.1)	35 (30.4)	0.657
Hypertension	33 (75.0)	85 (73.9)	0.889
CHD previous	7 (15.9)	39 (33.9)	0.025
Smoking			
• Smokers	19 (43.2)	71 (61.7)	0.035
• Non Smokers	25 (56.8)	44 (38.3)	
Family history of CHD	2 (4.5)	2 (1.7)	0.307
Dyslipidemia	12 (27.3)	36 (31.3)	0.620
Clinical spectrum of ACS, n(%)			
• STEMI	32 (72.7)	65 (56.3)	0.008
• NSTEMI	10 (22.7)	19 (16.5)	
• UAP	2 (4.5)	31 (27.0)	
CKMB, mean ± SD	180.56 ± 184.27	70.64 ± 86.10	0.007
Creatinine (mg/dL), rerata ± SD	1.62 ± 1.05	1.087 ± 0.44	0.005
Lipid parameters, rerata ± SD			
Cholesterol total (mg/dL)	185.31 ±45.47	183.75 ± 48.05	0.425
Triglycerides (mg/dL)	132.83 ± 55.30	120.18 ± 72.24	0.681
HDL (mg/dL)	44.24 ± 24.82	48.21 ± 23.06	0.369
LDL (mg/dL)	121,56 ± 44.29	116. 07 ± 45.97	0.498
sdLDL (mg/dL)	108.339 ± 37.94	105.54 ±45.97	0.705
Hospital treatment, n(%)			
Heparin	36 (81.8)	106 (92.2)	0.059
Beta blocker	28 (63.6)	92 (80.0)	0.032
Statin	41 (93.2)	113 (98.3)	0.130
Thrombolysis	9 (20.5)	17 (14.8)	0.387
PCI	22 (50)	30 (26.08)	0.021

SD: Standard Deviations, CHD: Coronary Heart Disease, STEMI: ST-segment elevation myocardial infarct, NSTEMI: non ST segment elevation myocardial infarct, UAP: Unstable Angina pectoris, CKMB: Creatine Kinase isoenzyme MB, HDL: High Density Lipoprotein, LDL: Low Density Lipoprotein, sdLDL: small dense low-density lipoprotein, PCI: Percutaneous Coronary Intervention, ACS: Acute Coronary Syndrome

Tabel 3. Prevalence ratio of MACE in high sLDL level among patients with ACS

	MACE		P value	PR (95 % CI)
	n	%		
High sdLDL level (≥ 108.08 mg/dL)	24	54.5	0.392	1.25 (0.75 – 2.066)
Low sdLDL level (< 108.08 mg/dL)	20	45.4		

sdLDL : small dense Low density Lipoprotein, MACE: Major Adverse Cardiac Event, PR : Prevalence ratio, 95% CI : 95% Confidence Interval

with ACS to predict MACE. Based on the receiver operating characteristic curve (ROC) the cut-off value was 108.08 mg/dL (Figure 1).

Subjects with sdLDL level ≥ 108.08 mg/dL belong to the group of high sdLDL and those with sLDL level < 108.08 mg/dL were classified in the group of low sdLDL. Table 3 showed that high levels of sdLDL had the prevalence ratio of 1.25 for the MACE among patients with ACS, however there were no statistically significance (p = 0392).

The level of sdLDL is a strong predictor of CHD event as compared to other parameters. Nevertheless, there has been no previous study that compared the levels sdLDL between MACE group and without MACE group patients with ACS. In the univariate analysis of this study, it was found that a history of previous coronary heart disease, smoking, clinical spectrum, gender, heparin, beta blockers, statins, PCI, CKMB and creatinine impacted MACE.

Results of multivariate analysis showed that the previous history of CHD, smoking behaviour, PCI treatment, increased CKMB level, and increased creatinine level were independently predict MACE. Level of sdLDL did not associate with occurence of MACE. Results of the analysis were shown in table 4.

Tabel 4. Multivariate analysis of variables that affect the MACE

Variable	OR (95% CI)	*p*
Previous history of CHD	3.53 (1.16-10.74)	0.026
Smoking	3.06 (1.27-7.39)	0.013
Clinical spectrum	1.09 (0.33- 3.67)	0.886
sdLDL	0.45 (0.18-1.12)	0.656
Heparin	1.81 (0.49- 6.57)	0.368
Beta blockers	2.43 (0.92-6.45)	0.073
Statins	0.69 (0.07-6.32)	0.741
PCI	0.09 (0.01-0.88)	0.039
CKMB	3.58 (1.48- 8.64)	0.005
Creatinine	6.94 (2.83-16.97)	0.000

CHD: Coronary Heart Disease, sdLDL: small dense Low Density Lipoprotein, PCI: Percutaneous Coronary Intervention, CKMB: creatine kinase isoenzyme MB, OR: odds ratio, 95% CI : 95% Confidence Interval, significant if p> 0.05

Discussion

The basic characteristics of the two groups did not differ statistically significant in terms of demographics, disease history and previous CHD risk factors, clinical spectrum of ACS and lipid parameters. This indicated that the results were not influenced by general characteristics of the study subjects. In this study, a cut-off point sdLDL concentration is 108.08 mg/dl. Value ≥ 108.08 mg/dL is considered high and <108 085 g / dl categorized as low between group. From previous studies the normal value sdLDL was 15.45 ± 5 mg/dL in healthy individual.[12] The level of sdLDL is also divided into high risk of CHD if sdLDL levels > 30 mg/dl, intermediates risk if sLDL level 21-30 mg/dl and the optimal range is < 21 mg/dl.[13] Lipoprotein and apolipoprotein abnormalities, especially sdLDL can cause endothelial dysfunction by interfering with the balance related vasodilation function of nitrite oxide, prostacyclin and thromboxane A2. In addition, they inversely correlated with HDL-platelet thrombus formation. Low HDL, therefore low levels of apoA-1, may increase the activity of platelet activating factor and initiated the thrombus formation.[14,15]Other variables were statistically significant related to the occurrence of MACE is CKMB levels upon hospital admission (p = 0.007). It is known that high levels of CKMB correlated to the size of myocardial infarction occurring, and the more extensive infarction, ventricular function is also getting bad result in increased risk MACE 10. The use of beta-blockers for the treatment MACE group was lower than that non- MACE group (63.6% vs 80 %) and the proportion of this difference was statistically significant (p = 0.032). In the ESC guidelines, beta blockers are recommended for immediate given to patients with ACS because it can reduce mortality.[16] In another study, beta blockers do not have the effect in lowering mortality, but can reduce the incidence of recurrent myocardial infarction and angina.[17] In this study, the use of beta blockers was lower in the MACE group and may affect the outcome of the study. Beta blockers are recommended for patients with UAP or NSTEMI, especially if there are hypertension and / or tachycardia. The proportion of revascularization with PCI were significantly higher in the group MACE compared to the group without MACE (50% vs 26.8%) (p = 0.021), possibly because the group MACE initial condition was worse so that more coronary intervention performed as compared to group without MACE. In accordance with previous theories that PCI procedures can reduce MACE. The strategy of invasive angiography is aimed at patients with high to very high risk and in this guideline is a class IA recommendation.[18] The result of the multivariate analysis showed that previously history of CHD increased the risk of MACE. This may be due to the presence of previous abnormalities of heart muscle which can aggravate the clinical condition of the patient during acute events and would increase the occurrence of MACE.

Smoking is also a factor that is increasing the incidence of MACE in this study. Multivariate analysis showed smoking can increase the incidence of MACE. Previous studies have shown that smoking damages blood vessels and affects all phases of atherosclerosis, since endothelial dysfunction until the ACS. Smoking toxin components and mechanisms involved in the onset of cardiovascular dysfunction is unclear, however smoking increases inflammation, thrombosis, and oxidation of LDL. Previous research data also showed exposure to smoking increases oxidative stress thus becoming potential mechanisms that initiate cardiovascular dysfunction.[19]

The results are consistent with the PCI as actions that provide good clinical outcomes for patients with ACS. Results of this study are also consistent with other research that states that the PCI decrease the incidence of MACE within 30 days.[20] Another factor that affects the MACE in this study is CKMB. Results of multivariate conveniently indicates CKMB provide almost fourfold the risk of the occurrence of MACE in ACS patients in this study. The CKMB is a marker of myocardial infarction. Patients with CKMB increase or more than 3 times the normal value has damaged blood vessels more and more likely to have coronary lesions type C, an average of more and longer stents were installed, as well as having clinical success are lower, so MACE more in patients with higher CKMB.[21] The study also found that CKMB is an independent factor affecting MACE, where MACE are more prevalent in the group with higher CKMB. In this study, creatinine also give effect to the MACE independently.

Several limitation were found in this study. Firstly, the varying levels of triglycerides and its association with glucose intolerance will affect the levels of sdLDL. In patients with glucose intolerance, sdLDLnya levels will be higher. This study could not detect the presence of glucose intolerance. Second, the study also did not include several confounding factors that may affect the lipid profile and insidence of MACE, such as previous medication, TIMI score, GRACE score, extent and location of infarction, previous ejection fraction, so the MACE incident analysis in this study is less detail.

Conclusion

From the results of this study, it was concluded that the levels of sdLDL, calculated from blood lipid value, did not associated with risk of MACE in patients hospitalised with ACS.

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