

# Potential of lipoproteins as biomarkers in acute myocardial infarction

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## ABSTRACT

Acute myocardial infarction (AMI), commonly known as heart attack, is a medical emergency that is potentially fatal if not promptly and properly managed. The early diagnosis of AMI is critically important for the timely institution of pharmacotherapy to prevent myocardial damage and preserve cardiac function. Ischemic insults during AMI cause myocardial tissue damage, releasing the cardiac muscle protein troponin T into the blood stream. Therefore, serum troponin T levels are used as a sensitive and specific indicator of myocardial injury for diagnosing AMI. However, there remains a requirement for developing technologies for more accurate biomarkers or signatures for AMI diagnosis or prognosis. Previous studies have implicated impaired lipid metabolism as a causative factor in AMI development. Lipoproteins are important constituents of lipid metabolism; their levels in the blood stream are a convenient biomarker tool for monitoring lipid metabolism. This review summarizes recent findings (data of studies from 2001 to 2016) regarding the biomarker potentials of various lipoproteins, including low-density lipoprotein, oxidized low-density lipoprotein, high-density lipoprotein, lipoprotein-a, and remnant lipoprotein, for the risk stratification of AMI. (*Anatol J Cardiol* 2017; 18: 68-74)

**Keywords:** myocardial infarction, circulating lipoproteins, lipid metabolism, biomarkers

## Introduction

The pathogenesis of acute myocardial infarction (AMI) is complex and multifactorial; however, several studies have suggested that impaired lipid metabolism plays an important role in AMI development (1, 2). A decrease in serum high-density lipoproteins (HDLs) (Fig. 1) and an increase in C-reactive proteins (CRPs) (Fig. 2) strongly predispose individuals at risk for an AMI event (1). Khan et al. (1) suggested the biomarker potential of HDL and CRP for assessing a combined lipid-inflammation risk factor that can be used as an important predictor of high-risk individuals and as a prognostic marker for AMI. Altered levels of carnitine, which is essentially required for transporting long-chain fatty acids into the mitochondrial matrix, where they are oxidized to produce energy, have been reported in AMI patients (3). Elevated blood carnitine levels in AMI patients have been attributed to the poor uptake or increased leakage of carnitine through the ischemic myocardium (4). The role of carnitine homeostasis in AMI was also supported by variations in blood carnitine levels owing

to the genetic polymorphism in the carnitine palmitoyltransferase gene (5). Khan et al. (6) observed a significant increase in total and differential leukocyte counts, which was significantly correlated with CRP levels, indicating a proinflammatory cascade in AMI patients. Monocytes were found to be significantly increased in AMI patients but not in infected controls; however, serum creatine kinase (CK) was significantly increased in AMI patients and was decreased in infected controls. These differential trends of monocytes and CK in AMI and infective controls could be used for the prognosis of AMI patients (7). The markers of the extrinsic and intrinsic pathways of coagulation such as prothrombin time and activated partial thromboplastin time were found to be significantly increased in AMI patients (8).

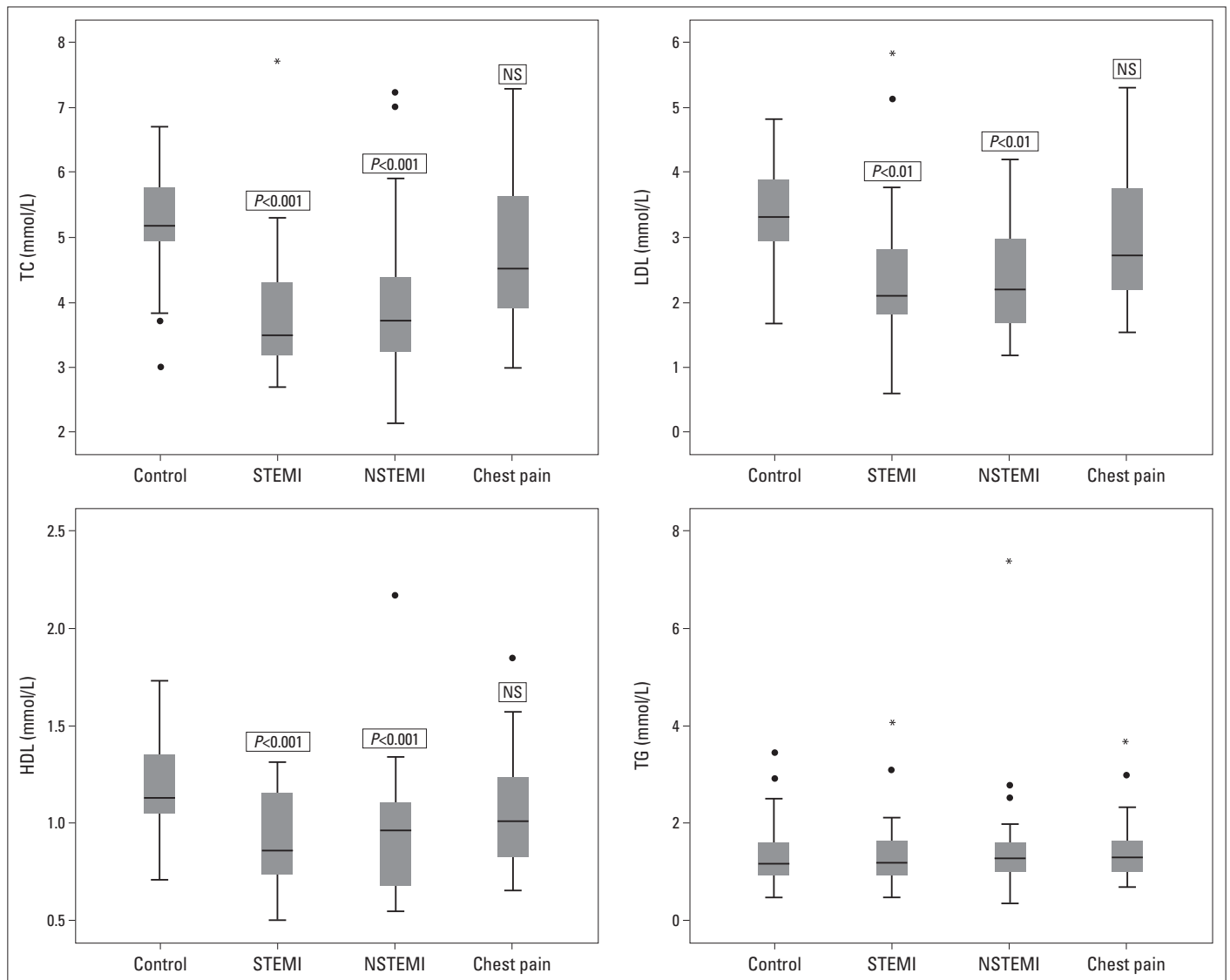
Serum lipid and lipoprotein levels change during the course of acute coronary syndrome (ACS) because of inflammatory responses. The levels of circulating lipids, including lipoproteins, are directly correlated with atherosclerotic plaque development. Excessive lipids also directly influence thrombosis and influence the risk and outcome of acute cardiovascular events. Plasma li-

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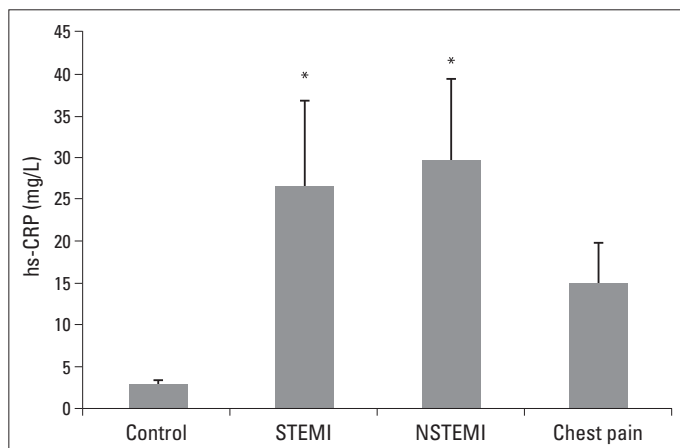
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**Figure 1.** Box plots showing lipid profile (TC, LDL, HDL, and TG) in healthy controls and AMI patients (STEMI and NSTEMI) and chest pain. Values are given as medians and 25%–75% interquartile range; outliers and extremes are shown as filled circles and stars respectively. *P* values versus the control group using Dunnett’s test. Reproduced from Khan et al. (1) under Creative Commons Attribution License



**Figure 2.** Serum hs-CRP levels in different groups.\**P* < 0.05 versus the control group using Dunnett’s test. Reproduced from Khan et al. (1) under Creative Commons Attribution License

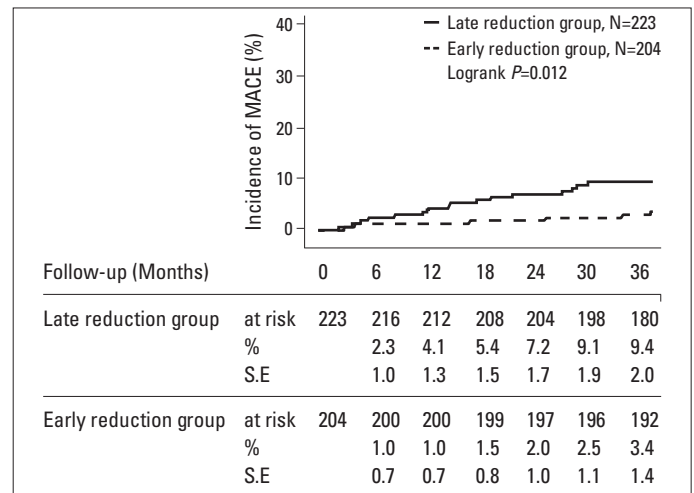
poproteins influence three aspects that are important for atherothrombosis: endothelial function, platelet aggregation (primary coagulation), and secondary coagulation. Shrivastava et al. (9) investigated 400 AMI patients who were admitted within 24 h of symptom onset. The results of the lipid profile indicated a trend of reduced total cholesterol (TC), low-density lipoproteins (LDLs), and HDL and elevated triglyceride (TG) levels between day 1 and day 2 serum samples of AMI patients; however, corrections of serum lipid levels were observed at day 7. In a series of 67 AMI patients, TC and LDL levels significantly decreased (9%) in the 24 h after admission and by 13% and 17%, respectively, on day 4, whereas HDL and TG levels did not significantly change (10). The independent predictors of LDL decrease were diabetes mellitus and elevated cardiac troponin T levels. It was recommended that only measurements taken within 24 h of AMI onset should be used as a guide for selecting lipid-lowering medication (10).

Although lower TC, LDL, and HDL levels have been reported in AMI, it is associated with acute inflammatory reaction during the rupture of atherosclerotic plaques; hence, lipid-lowering therapy should not be delayed for treating AMI patients with lower lipid levels (11). Among patients with ACS who were effectively treated with statins, fasting TG predicted long- and short-term cardiovascular risk, suggesting that TG-rich lipoproteins are important additional targets for therapy (12). Using the average 5.5-years follow-up data of 4827 male subjects aged  $\geq 40$  years from the general population with no cardiovascular history, no use of lipid-lowering agents, and with LDL levels of  $<120$  mg/dL, it was observed that non-HDL cholesterol, TC/HDL, and LDL/HDL ratios can predict residual risks for AMI or sudden death (13). This review summarizes the recent studies regarding biomarker potentials of various lipoproteins, including LDL, oxidized LDL (Ox-LDL), HDL, lipoprotein-a [Lp(a)], and remnant lipoprotein (RPL) for risk stratification of AMI.

### LDLs

Miura et al. (14) evaluated the effect of early reduction of LDL levels for secondary prevention of AMI by comparing the target LDL reduction of  $\geq 30\%$  was achieved and not reached within 4 weeks after randomization in 204 cases (early reduction group) and 223 cases (late reduction group). They observed that major adverse cardiovascular events were significantly more frequent in the late reduction group (9.4%) than in the early reduction group (3.4%). The incidence of cardiac deaths was also significantly higher in the late reduction group (3.1%) than in the early reduction group (0.5%), suggesting that rapid reduction of LDL levels is strongly associated with favorable outcomes in AMI patients (Fig. 3) (14). Reddy et al. (15) studied the association between lipid levels and in-hospital all-cause mortality in 115,492 patients hospitalized for AMI using multivariable-adjusted logistic regression models. Compared with the lowest quartile of LDL ( $<77$  mg/dL), the risk for in-hospital mortality in the second to fourth quartiles decreased, indicating a lipid paradox, with lower LDL levels associated with an increased risk for in-hospital mortality, contrary to findings outside the acute setting (15).

Survival analysis and Cox proportional hazard analysis of stratified AMI patients with their LDL levels above (501 patients) or below (575 patients) the median level showed that LDL levels on admission had no significant effect on the 6-month and 1-year incidence of major adverse cardiac events (MACEs), but the incidence of MACE was significantly higher in the low LDL group at 1 month than at 1 year (16). In another study of 562 AMI patients, the 3-month LDL decrease of  $<40\%$  was identified to be a significant risk factor for predicting 5-year cardiovascular death, whereas patients with the 3-month LDL decrease of  $\geq 40\%$  had a higher rate of freedom from MI and lower cardiovascular mortality, although these patients had higher baseline LDL values (17). A persistent decline in LDL-cholesterol levels preceded the development of rheumatoid arthritis (18) and was also inversely correlated with atrial fibrillation (19).



**Figure 3.** Incidence of major adverse cardiac events (MACEs) between patients in the late and early LDL reduction groups. *Reproduced from Miura et al. (14) under Creative Commons Attribution License*

Chappey et al. (20) screened 160 hypercholesterolemic subjects who were free of cardiovascular diseases for carotid, aortic, and femoral plaques and for coronary calcifications to investigate the association between LDL sialic acid levels and the prevalence of these early atherosclerotic lesions. Their results suggest that LDL sialic acid content is not a discriminant marker of early atherosclerosis in asymptomatic hypercholesterolemic subjects. However, in a later study by the same investigators, LDL sialic acid content was found to be significantly higher in AMI patients than in healthy controls, suggesting that LDL sialic acid levels increase with the extension of atherosclerosis and its progression to acute complications (21).

### Ox-LDLs

Ox-LDL plays a key role in proinflammatory process associated with atherosclerosis progression. Patients with high Ox-LDL and high-sensitivity C-reactive protein (hs-CRP) levels were more likely to develop AMI or die than those with either elevated Ox-LDL or hs-CRP levels. Receiver operating characteristic curves showed that Ox-LDL and hs-CRP have higher sensitivity and specificity than those of troponin T for predicting AMI or death (22). Napoleao et al. (23) observed that plasma Ox-LDL levels were significantly higher in AMI patients in the acute phase relative to reference levels, which progressively decrease over the recovery period. Ehara et al. (24) noticed that plasma Ox-LDL levels were significantly higher in AMI patients than in stable angina pectoris (SAP) patients, whereas total coronary calcium score and total calcium area were significantly smaller in AMI patients than in SAP patients. Kayo et al. (25) reported a significant association between plasma Ox-LDL levels and coronary plaque instability in AMI patients. Ox-LDL levels showed a significant positive correlation with the severity of ACSs, and more severe lesions also contained a significantly high percentage of Ox-LDL-positive macrophages (26). The Ox-LDL/TC ratio

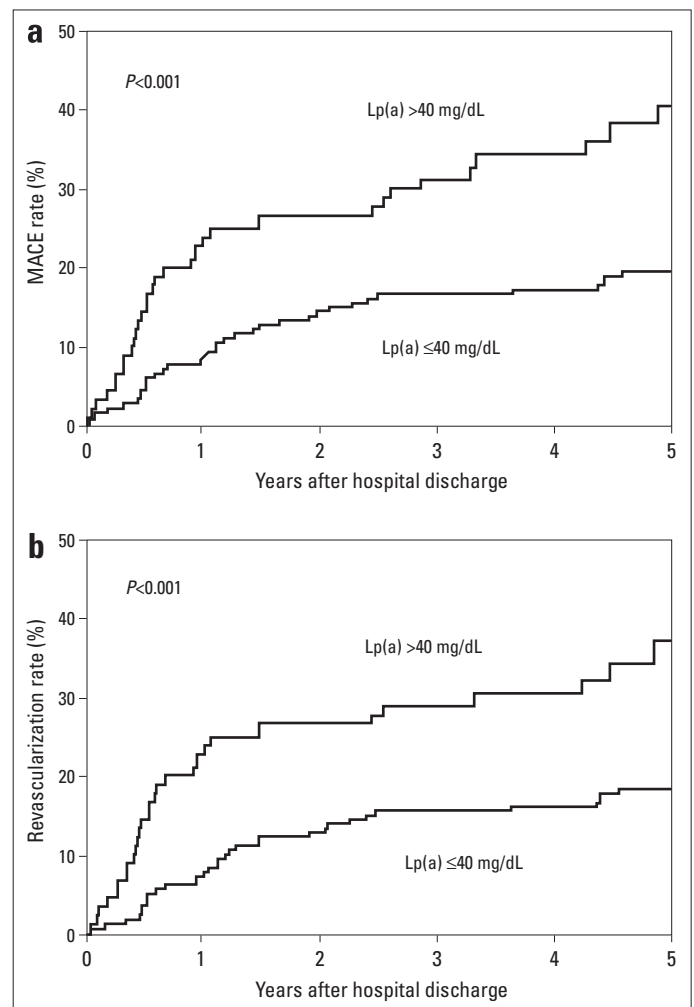
was significantly higher in AMI patients than in healthy controls and hypercholesterolemic controls, suggesting that high plasma Ox-LDL/TC ratio was an indicator of increased risk for AMI (27).

## HDLs

Ji et al. (28) evaluated the effect of low HDL levels on clinical outcomes in ST-segment elevation myocardial infarction (STEMI) patients compared with non-ST-segment elevation myocardial infarction (NSTEMI) patients. Low HDL levels were associated with significantly higher risks for in-hospital mortality in STEMI patients but not in NSTEMI patients; thus, a more aggressive treatment should be considered in STEMI patients with low HDL levels (28). In this post-hoc analysis of 2193 stable ischemic heart disease patients, the patients continued to experience incremental cardiovascular risk associated with low HDL levels despite optimal medical therapy during long-term follow-up. This association persisted and appeared more prominent even when LDL levels were reduced to optimal levels using an intensive lipid-lowering therapy. In a cross-sectional study of 295 Saudi patients who underwent coronary angiography, low HDL levels were the most frequent lipid abnormality observed, which significantly affected the extent of coronary artery disease (CAD) (29). However, there is insufficient evidence from clinical trials to recommend HDL-targeted therapy for additional event reduction in CAD patients (30).

Lee et al. (31) examined 3574 AMI patients with follow-up records of HDL levels to investigate its association with clinical outcomes, with the primary endpoint being the association between follow-up change in HDL levels and a 12-month composite of MACEs. Patients with initial HDL levels of  $\geq 40$  mg/dL showed significantly lower rates of 12-month MACEs, particularly cardiac and all-cause mortalities (Fig. 4). Stratification of patients according to HDL change showed that patients with decreasing HDL had significantly higher rates of 12-month MACEs compared with those with increasing HDL levels; a multivariate analysis indicated that HDL levels were a significant predictor of cardiovascular events after correcting for confounding variables (31). Although statin therapy moderately increases HDL levels, a paradoxical decrease in HDL levels after statin therapy in some patients might be an independent predictor of long-term adverse cardiovascular events in AMI patients (32).

Albers et al. (33) recently demonstrated that HDL3 cholesterol levels, but not other lipoprotein fractions, are predictive of future cardiovascular events, suggesting that the HDL3 subclass is primarily responsible for the inverse association of HDL and cardiovascular diseases. Khan et al. (1) showed that a decrease in serum HDL levels and an increase in hs-CRP levels strongly predispose individuals at a risk for an AMI event, emphasizing on the importance of HDL and CRP levels for assessing a combined lipid-inflammation risk factor that could be a useful predictor of high-risk individuals, as well as a prognostic marker in AMI patients.



**Figure 4.** Kaplan–Meier curve showing the effect of initial HDL levels on the prevalence of 1-year major adverse cardiac events (MACEs). *Reproduced from Lee et al. (31) under Creative Commons Attribution License*

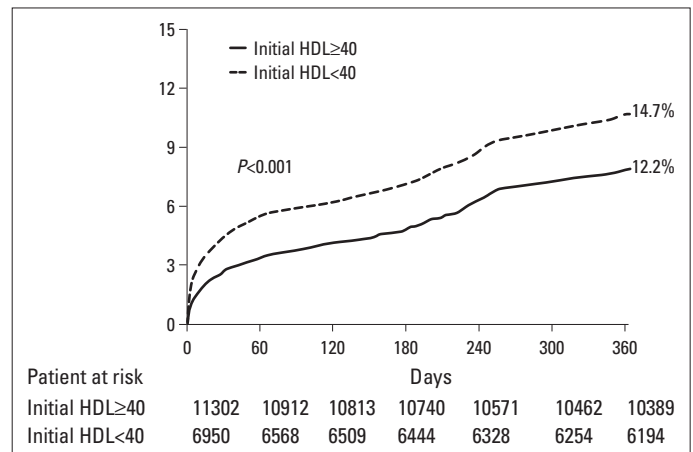
## Lp(a)

Lp(a) is a subclass of lipoproteins that has recently become an important biomarker because of its association with cardiovascular diseases. Lp(a) inhibits the fibrinolysis system and promotes thrombus formation. The structure of Lp(a) is quite similar to that of plasminogen; hence, it competes with plasminogen for a binding site, leading to reduced fibrinolysis. On binding to clots, plasminogen is converted into active plasmin by various enzymes, including tissue plasminogen activator (tPA) and urokinase plasminogen activator (uPA). Because Lp(a) stimulates the secretion of the plasminogen activator inhibitor-1 (PAI-1), it leads to thrombogenesis as the main function of PAI-1 is to inhibit uPA, an enzyme responsible for the cleavage of plasminogen to plasmin. A combination of tPA and PAI-1 has been suggested to be useful for assessing AMI prognosis (34). In addition, Lp(a) transports the more atherogenic proinflammatory-oxidized phospholipids, which attract inflammatory cells to vessel walls and leads to smooth muscle cell proliferation that facilitates plaque build up (35).

Ikenaga et al. (36) measured Lp(a) levels 1 week after AMI and divided the patients into two groups based on high Lp(a) ( $>40$  mg/dL) and low Lp(a) ( $\leq 40$  mg/dL) levels. The incidence of MACE during 5 years was significantly higher in the high Lp(a) group than in the low Lp(a) group (Fig. 5). This difference was primarily driven by a higher incidence of new lesions that required revascularization in the high Lp(a) group (36). Cho et al. (37) measured serum Lp(a) levels in 832 consecutive AMI patients on admission and divided them into tertiles according to serum Lp(a) levels: Lp(a) levels of  $<13.8$ ,  $13.8$ – $30.6$ , and  $>30.6$  mg/dL. The risk estimate for MACEs at the 1-year follow-up was significantly higher in tertile 3 than in tertiles 1 or 2, suggesting that high serum Lp(a) levels were significantly associated with long-term adverse outcomes after AMI (37).

Morita et al. (38) determined serum Lp(a) levels in 130 AMI patients who underwent direct percutaneous coronary intervention and classified the patients on the basis of Lp(a) levels at 1 month after AMI onset into two groups, namely high Lp(a) ( $\geq 30$  mg/dL) and low Lp(a) ( $<30$  mg/dL), for evaluating the clinical coronary stenosis progression (CCSP) rate. The findings showed that high serum Lp(a) levels were a significant risk factor for CCSP but did not influence restenosis after stenting. Lp(a) levels have been found to be significantly higher in patients with persistent occlusion than in those with spontaneous recanalization of infarct-related arteries in the early AMI phase (39). Motta et al. (40) observed a positive correlation between mean serum Lp(a) levels on days 1 and 7 and the size of the necrotic area in AMI patients, suggesting that Lp(a) has an atherogenic and prothrombotic role. Elevated Lp(a) levels are closely associated with the increase in the early morning incidence of AMI via a change in the prothrombotic state (41). Elevated serum Lp(a) levels were associated with a history of prior MI in coronary spasm patients, suggesting that Lp(a) plays an important role in the genesis of thrombotic coronary occlusion and the occurrence of AMI subsequent to coronary spasm (42).

Postorino et al. (43) evaluated that the association between serum Lp(a) levels and AMI and cerebral vasculopathies (CVP) in elderly patients. The average serum Lp(a) level was 40.8 mg/dL in AMI patients, 46.7 mg/dL in CVP patients, and 23.2 mg/dL in healthy controls, suggesting that an increased Lp(a) level has diagnostic value for the presence of both AMI and CVP and also represents a risk factor for developing CVP (43). Nomura et al. (44) determined serum Lp(a) levels in 87 AMI patients, 49 cerebrovascular disease (CVD) patients, and 85 healthy controls and correlated the levels with lesions in the coronary and cerebral arteries. These results showed that high Lp(a) levels were linked to atherosclerosis of the cerebral and coronary arteries and influenced the disease severity. In a meta-analysis, adjusted for age and sex only, there were continuous associations of Lp(a) levels with the risk for coronary heart disease (CHD), potentially consistent with either a curvilinear or log-linear shape of the risk curve (45). The risk ratio for CHD per 3.5-fold higher Lp(a) level, adjusted for age and sex only, was 1.16 [95% confidence interval



**Figure 5.** (a) Major adverse cardiac event (MACE) after hospital discharge in patients with high or low Lp(a) levels. (b) Revascularization for new lesions in patients with high or low Lp(a) levels. Reprinted from Ikenaga et al. (36) after permission from J-Stage

(CI), 1.11–1.22] and 1.13 (95% CI, 1.09–1.18), respectively, after further adjustments for systolic blood pressure, smoking, history of diabetes, and total cholesterol. These findings indicated that under a wide range of circumstances, there were continuous, independent, and modest associations of Lp(a) levels with the risk for CHD and stroke that appeared exclusive to vascular outcomes (45). However, Lp(a) levels were not a risk factor for left ventricular thrombus in AMI patients (46). Mora et al. (47) observed an inverse association between Lp(a) levels and the risk for type-2 diabetes, which was independent of risk factors.

## RLPs

RLPs are partially hydrolyzed, TG-rich lipoproteins that are potentially atherogenic and are associated with early onset AMI. The occurrence of AMI in young individuals ( $\leq 40$  years) represents a rare disease with a typical risk factor profile and a lipid phenotype that is characterized by a predominance of elevated TG-rich lipoproteins. Non-HDL cholesterol is most strongly associated with premature AMI and can serve as a preferred risk predictor and therapeutic target in a young patient population (aged  $\leq 40$  years) (48). RLP may be defined as intermediate-density lipoprotein cholesterol plus very-low-density lipoprotein cholesterol subfraction 3 (49). A prospective case-control study with 302 AMI patients (aged  $\leq 40$  years) and 200 healthy controls showed that remnant cholesterol was 1.7-fold higher in premature AMI patients than in healthy controls. Remnant cholesterol was the lipid fraction most strongly associated with premature MI (odds ratio, 3.87), suggesting it as a new potent risk marker in a young patient population (50). Martin et al. (49) prospectively examined 2465 AMI survivors aged  $58 \pm 12$  years and concluded that higher RLP levels were associated with lower mortality 2 years after AMI, despite rigorous adjustment for known confounders, implying that unknown protective factors or a lead-time bias likely explains the paradox. However, the investigators

did not rule out the possibility that higher RLP cholesterol levels are associated with increased mortality at intervals of >2 years after AMI, when the long-term atherogenic effects of RLP cholesterol are more likely to result in cardiovascular events (49).

## Conclusion

Impaired lipid metabolism plays an important role in the pathogenesis of cardiovascular disease. Because lipoproteins are the primary constituents of lipid metabolism, their serum levels are convenient biomarker tools that reflect the lipid metabolic pattern and thus can be used for risk stratification and AMI prognosis. A high LDL level is a risk factor for AMI, whereas a rapid reduction of the LDL level is strongly associated with favorable outcomes in AMI patients. Ox-LDL plays a key role in the proinflammatory process associated with the progression of atherosclerosis, with a strong association between Ox-LDL levels and coronary plaque instability in AMI patients. Plasma Ox-LDL levels tend to be significantly high in AMI patients in the acute phase and progressively decrease over the recovery period. A decreased serum HDL level strongly predisposes individuals at risk for an AMI event. Low HDL levels are significantly associated with a high risk for in-hospital mortality in AMI patients. Lp(a) measurements may provide more details regarding the risk for AMI; however, the added value of this biomarker beyond a routine lipid profile remains to be standardized. Remnant lipoproteins are potentially atherogenic and are associated with early-onset AMI, suggesting it as a new potent risk marker in the young patient population.

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