Serum Malondialdehyde-modified Low-density Lipoprotein Levels on Admission Predict Prognosis in Patients with Acute Coronary Syndrome Undergoing Percutaneous Coronary Intervention

Naofumi Amioka, MD[a)]; Toru Miyoshi, MD, PhD[a)]; Hiroaki Otsuka, MD[a)]; Daisuke Yamada, MD[b)]; Atsushi Takaishi, MD, PhD[c)]; Masayuki Ueeda, MD, PhD[c)]; Satoshi Hirohata MD, PhD[d)]; Hiroshi Ito, MD, PhD[a)]

[a]Department of Cardiovascular Medicine, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama City, Japan

[b]Department of Cardiology, Onomichi Municipal Hospital, Onomichi City, Japan

[c]Department of Cardiology, Mitoyo General Hospital, Kanonji City, Japan

[d]Department of Medical Technology, Okayama University Graduate School of Health Sciences, Okayama City, Japan

Corresponding author: Toru Miyoshi, MD, PhD

e-mail: miyoshit@cc.okayama-u.ac.jp

Mailing address: Department of Cardiovascular Medicine, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, 2-5-1 Shikata-cho, Kita-ku, Okayama City, 700-8558, Japan.

Keywords: coronary artery disease, percutaneous coronary intervention, oxidized low-density lipoprotein, prognosis

Abstract

Background: Malondialdehyde-modified low-density lipoprotein (MDA-LDL) is a predictive marker of cardiovascular events in patients with stable angina pectoris. However, little is known about this marker in patients with acute coronary syndrome (ACS). We investigated the prognostic relevance of MDA-LDL to cardiovascular outcomes in patients with ACS.

Methods: A total of 370 consecutive patients with ACS who underwent primary percutaneous coronary intervention (PCI) were enrolled from October 2009 to September 2014 at Mitoyo General Hospital. Serum MDA-LDL levels were examined at admission. The patients were divided into three groups according to tertile value of serum MDA-LDL levels. The primary outcomes were cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, revascularization, and heart failure requiring hospital admission.

Results: MDA-LDL levels in patients with acute myocardial infarction were significantly greater than those in patients with unstable angina pectoris (mean ± standard deviation: 133±48 U/L vs 157±69 U/L, p=0.001). During follow-up (472 [195–920] days), 82 (22%) events occurred. Kaplan–Meier analysis showed that patients in the highest MDA-LDL tertile had the worst prognosis (log-rank, $p<0.001$). Cox regression analysis showed that serum MDA-LDL levels were an independent predictor of cardiovascular events after PCI in patients with ACS, even after adjustment for age, sex, body mass index, conventional cardiovascular risk factors, other lipid biomarkers, statin use on admission, cardiac biomarkers, and presence or absence of multivessel disease (hazard ratio: 1.80 per 1 standard deviation U/L increase, 95% confidence interval: 1.07–3.16, $p=0.027$). Conclusion: Serum MDA-LDL levels on admission are a significant prognostic marker in patients with ACS who undergo successful PCI.

Introduction

Accumulating evidence has shown that oxidized low-density lipoprotein (LDL) is a useful marker for cardiovascular disease. Oxidized LDL contributes to atherogenesis in a wide range of stages, such as impairing vascular endothelial cells, promoting expression of adhesion factors of vascular endothelial cells, and facilitating monocyte migration and accumulation of lipids under the vascular endothelium through being captured by macrophages [1]. Previous studies have shown that oxidized LDL levels are elevated in patients with coronary artery disease [2,3]. Oxidized LDL levels are especially increased in acute coronary syndrome (ACS) compared with stable angina pectoris [4]. Furthermore, elevated oxidized LDL levels are predictive of future cardiovascular events in healthy men and predict an increased risk of future myocardial infarction in apparently healthy people [5]. These reports suggest that oxidized LDL is not only a promoter of atherogenesis, but is also an important marker for the severity of cardiovascular disease and a predictor of future cardiovascular events.

Malondialdehyde-modified low-density lipoprotein (MDA-LDL) is one of the major products of lipid peroxidation and the most common formation of oxidized LDL. Similar to oxidized LDL, many reports have shown that MDA-LDL is an important marker for reflecting the severity of cardiovascular disease [6]. MDA-LDL is also a predictor of future cardiac events in patients with stable angina pectoris who undergo percutaneous coronary intervention (PCI) [7]. Furthermore, MDA-LDL levels are a predictive factor for in-stent restenosis in patients with type-2 diabetes with old myocardial infarction or stable angina pectoris after PCI [8]. However, little is known about the effect of MDA-LDL on the prognosis of patients with ACS. Therefore, this study aimed to investigate whether MDA-LDL levels predict cardiovascular events in patients with ACS after successful PCI.

Materials and Methods

This was a retrospective, single-center study that included patients with ACS who underwent successful PCI from October 2011 to September 2014 at Mitoyo General Hospital. We defined

ACS as patients with acute myocardial infarction or unstable angina pectoris. Acute myocardial infarction was defined as type 1 according to the Third Universal Definition of Myocardial Infarction [9]. Unstable angina pectoris was defined when patients had unstable symptoms of chest pain (at rest/severe and new onset/crescendo pattern), and there was no detectable release of enzymes and biomarkers of myocardial necrosis, with or without changes in electrocardiography. A successful PCI was defined, according to the definition of angiographic and procedural success in the 2011 ACCF/AHA/SCAI PCI guideline [10].

The exclusion criteria of this study were as follows: stable angina pectoris; no available data on MDA-LDL; previous PCI or coronary artery bypass graft surgery performed within 6 months; allergy or contraindication to antiplatelet agents or contrast media; cardiogenic shock or receiving cardiopulmonary resuscitation; comorbid conditions associated with a life expectancy of <1 year; and inadequate oral medical treatment therapy, including beta-blockers, renin–angiotensin–aldosterone system inhibitors, and statins after PCI.

After screening 773 patients, 403 were excluded. We excluded 345 patients with stable angina pectoris, 8 without successful PCI, 8 without available data of MDA-LDL, 6 with a previous history of PCI or coronary artery bypass grafting performed within 6 months, 8 with cardiogenic shock, and 28 without adequate oral medical treatment therapy after PCI. A total of 370 patients with ACS met the criteria and were included in this study (Figure 1).

We examined the impact of MDA-LDL for prognosis of patients with ACS in main study, with comparing among three groups according to tertile value of serum MDA-LDL levels by using following way of analysis. Furthermore, as sub-study, we re-examined the impact of MDA-LDL for only patients with acute myocardial infarction by comparing two groups according to the median value of serum MDA-LDL levels.

This study was approved by the institutional ethics committee of Mitoyo General Hospital. All patients provided written informed consent for enrolment in this study. This study was conducted according to the principles expressed in the Declaration of Helsinki.

All patients underwent PCI by a 6Fr or 7Fr guiding catheter. The patients received dual antiplatelet agents and 7000 IU of unfractionated heparin just before the procedure, and an additional bolus of heparin was administrated during PCI to achieve a target activated clotting time >250 seconds every 1 hour. Patients received an intracoronary optimal dose of isosorbide dinitrate before coronary angiography (CAG), to prevent coronary spasm, as long as there was no hemodynamic instability. Balloons and stents were used depending on the operator's decision. The operator also decided the position and length of the angioplasty according to angiographic and intravascular ultrasound findings.

The patients received optimal medical therapy, such as dual antiplatelet agents and statins after PCI, based on Japanese and American College of Cardiology/American Heart Association guidelines [11,12].

Venous blood samples were collected just before PCI. MDA-LDL levels were measured using an enzyme-linked immunosorbent assay (Sekisui Medical Co., Tokyo, Japan) on the basis of the same principles reported by Kotani et al [13]. For MDA-LDL measurement, inter- and intra-coefficient variants were 6.5% and 9.0%, respectively [14]. Other laboratory parameters were measured using standard laboratory techniques with an automatic analyzer.

The primary endpoint of this study was major adverse cardiac and cerebrovascular events (MACCE), including cardiovascular death, non-fatal myocardial infarction, non-fatal stroke (ischemic or hemorrhagic), ischemia-driven revascularization, and heart failure requiring hospital admission. Coronary revascularization was performed only for severe stenosis (≧90%) or if significant myocardial ischemia was proven with an objective modality (i.e., myocardial scintigraphy or invasive fractional flow reserve) during follow-up time [15]. We did not treat scheduled PCI for residual lesion as revascularization event in this study. Follow-up data were collected by a blinded assessment team with no information on the background of the patients (H.O. and D.Y.).

Standard statistical methods were used in this study. Background data are expressed as mean ± standard deviation for normally distributed continuous variables or median (interquartile range for non-normally distributed continuous variables. We used Student's t-test (between two groups) or one-way analysis of variance (among three groups) for comparing normally distributed continuous variables, and Bonferroni correction was used for post-hoc testing. For continuous variables with a non-normal distribution, Wilcoxon rank sum test (between two groups) or Kruskal–Wallis test (among three groups) were used to examine differences in medians. Discrete variables are presented as percentages and frequencies; comparisons were based on the chi-square test. The Kaplan–Meier method was used to estimate cumulative adverse events and significance was evaluated by using the log-rank test. Cox proportional hazard models were used to analyze the relationship of serum MDA-LDL levels and event-free survival after adjustment for age, sex, body mass index, and the prevalence of coronary risk factors (hypertension, diabetes mellitus, dyslipidemia, and smoking), other lipid biomarkers, statin use on admission, and cardiac biomarkers, including peak creatine phosphokinase, brain natriuretic peptide, and presence or absence of multivessel disease. Logarithmic transformation was also used for non-normally distributed continuous variables to transform them to normally distributed continuous variables when we put them into Cox proportional hazard models. A receiver operating characteristic curve was constructed to demonstrate the discriminatory power of MDA-LDL levels for pre-specified cardiovascular outcome. Variables were considered as significant when $p<0.05$. We performed all analyses in this study using JMP version 9.0 (SAS Institute, Tokyo, Japan) or IBM SPSS Statistics version 24 (IBM Corp., Armonk, NY, USA).

Results

In main analysis, patients with ACS (n=370) were divided into tertile groups according to serum MDA-LDL levels (U/L), with the lowest tertile at ≤118 (n=124), the middle tertile at 119–160 (n=123), and the highest tertile at ≥161 (n=123).

The baseline characteristics of the study population are shown in Table 1. The mean age was 71±11 years old and 282 (76%) patients were men. Patients in the highest MDA-LDL group were younger and the percentage of smokers (former or current) was significantly higher compared with those in the other tertile groups. Body mass index was significantly higher in the highest

MDA-LDL group compared with the lowest MDA-LDL group. Furthermore, although the highest MDA-LDL tertile group had a higher prevalence of dyslipidemia, they received significantly less statin therapy on admission compared with the other 2 groups. With regard to the lipid profile, levels of triglyceride, total cholesterol, and low-density lipoprotein cholesterol (LDL-C), the ratio of LDL-C to high-density lipoprotein cholesterol (HDL-C), and the ratio of MDA-LDL to LDL-C (MDA-LDL/LDL-C ratio) were significantly higher in the highest MDA-LDL tertile group compared with the other 2 groups. The ratio of acute myocardial infarction was highest in the highest MDA-LDL tertile group, but the ratio of unstable angina pectoris was highest in the lowest MDA-LDL tertile group. MDA-LDL levels in patients with acute myocardial infarction (n=264) were significantly higher than those in patients with unstable angina pectoris (n=106) (133±48 U/L vs 157±69 U/L, p=0.001).

We performed follow-up CAG for 232 (63%) patients, 6-12 months after PCI (Figure 2). Then we performed PCI for 31 patients with severe coronary artery stenosis, and 3 patients with 75-90% coronary artery stenosis showing positive result in myocardial scintigraphy. We did not performed PCI for 6 patients with 75-90% stenosis showing negative result in myocardial scintigraphy (n=5), or fractional flow reserve (n=1). Most patients (n=192) did not show significant stenosis in follow-up CAG. On the other hand, 138 (37%) patients did not receive follow-up CAG, and the detailed reasons of those are shown on Online Table 1. There was no significant difference among three groups in the ratio of patients without follow-up CAG (Table 1), and in the ratio of each detailed reasons for not undergoing follow-up CAG (Online Table 1).

During the follow-up (median [interquartile range]: 472 [195–920] days), 82 (22%) MACCE occurred (Table 2). The incidence of MACCE was highest in the tertile group with the highest MDA-LDL levels, followed by the middle and the lowest tertile groups (lowest group: 12, middle group: 30, highest group: 40, p<0.001). The number of revascularizations for angina pectoris (49 events) was highest among MACCE events, and the highest MDA-LDL tertile group showed the greatest number of events, followed by the middle and the lowest tertile groups (lowest group: 3, middle group: 17, highest group: 29, p<0.001). There were no other significant differences in any type of events among the 3 groups.

Kaplan–Meier curves for each of the 3 groups after PCI showed a poorer event-free survival rate in patients with the highest tertile of MDA-LDL levels, followed by the middle and the lowest tertile (log-rank, $p<0.001$, Figure 3A). However, there were no significant differences in other lipid biomarkers, such as total cholesterol, LDL-C, HDL-C, and triglyceride levels, among the tertile groups (Figure 3B–E).

Multivariate Cox regression analysis showed that serum MDA-LDL level on admission was an independent predictor for MACCE after PCI in patients with ACS (hazard ratio: 1.80 per 1 standard deviation [37 U/L] increase, 95% confidence interval: 1.07–3.16, p=0.027) after adjustment for age, sex, body mass index , conventional cardiovascular risk factors (hypertension, diabetes mellitus, dyslipidemia, and history of smoking), other lipid biomarkers, statin use on admission, and cardiac biomarkers, including peak creatine phosphokinase, brain natriuretic peptide, and presence or absence of multivessel disease (Table 3).

The specificity and sensitivity of the correlation between MACCE and serum MDA-LDL levels were evaluated using receiver operating characteristic analysis to assess their predictive value. Receiver operating characteristic analysis showed that the optimal cut-off level of MDA-LDL levels was 135 U/L and the area under the curve was 0.66 (95% confidence interval: 0.60–0.73). The predictive sensitivity and specificity of MDA-LDL levels were 76% and 56%, respectively.

Additionally, we showed the characteristics of patients with acute myocardial infarction (sub-study) in Table 4. As similar as main study, the higher MDA-LDL group (≤141 U/L) (n=130) showed younger age, higher body mass index, higher prevalence of dyslipidemia and poorer lipid profiles significantly, comparing to the lower MDA-LDL group (≥142 U/L) (n=134). Moreover, the prevalence of multi-vessel disease was higher in the higher MDA-LDL group, comparing to the lower MDA-LDL group.

The comparison of clinical events between these two group during follow-up time (433 [186–858] days) is shown in Online Table 2. As similar to main study, the incidence of MACCE (n=41 [31%]), and especially revascularization (n=28 [21%]) were significantly higher in the higher MDA-LDL group, comparing to those of the lower MDA-LDL group (n=14 [11%]) (n=6 [5%]) ($p<0.001$, respectively).

Kaplan–Meier curves shows a poorer event-free survival rate in patients with the higher MDA-LDL group, comparing to the lower MDA-LDL group (Online Figure 1).

After adjustment for same factors as main study, multivariate Cox regression analysis showed that serum MDA-LDL levels on admission was an independent predictor for MACCE after PCI even in patients with acute myocardial infarction (hazard ratio: 3.50 per 1 standard deviation [69 U/L] increase, 95% confidence interval: 1.27–10.5, p=0.016) (Table 5).

Discussion

The major findings of this study were as follows. (1) MDA-LDL levels in patients with acute myocardial infarction were higher than those in patients with unstable angina pectoris. (2) Elevation of serum MDA-LDL levels could be an independent predictor for MACCE in patients with ACS undergoing successful PCI. (3) The impact of MDA-LDL on prognosis had been also demonstrated, even if it is limited to patients with acute myocardial infarction. To the best of our knowledge, this is the first study to demonstrate the relation between serum MDA-LDL levels and prognosis after successful PCI in patients with ACS.

Serum MDA-LDL levels are a useful biomarker for reflecting the severity of coronary artery disease [2,16] and the presence of vulnerable plaques [17-19]. Our study showed that the acute myocardial infarction rate was higher, and the unstable angina pectoris rate was lower in patients with elevated MDA-LDL levels. These results support the clinical utility of MDA-LDL as a biomarker for reflecting the severity of coronary artery disease. Serum oxidized LDL levels, including MDA-LDL, reflect the presence of vulnerable plaques, but this is a systemic, not focal, effect. Therefore, elevated MDA-LDL levels might be the result of vulnerable plaques of other areas, such as the carotid artery, brain vessels, and arteries of the lower limbs. Additionally, our study showed poorer lipid balance and a higher body mass index in the highest MDA-LDL tertile group. Recent studies have shown that MDA-LDL levels show positive correlations with LDL-C and triglyceride levels, and a negative correlation with HDL-C levels [20-22]. Furthermore, Holvoet et al reported that hyperinsulinemia and impaired glycemic control, reflecting the severity of metabolic syndrome, were associated with increased *in vivo* LDL oxidation [23]. Our results are in good agreement with these previous reports.

The MDA-LDL/LDL-C ratio, which is an indicator of the extent of LDL oxidation, was higher in patients with elevated MDA-LDL levels, especially in the highest tertile. Other reports have shown that in addition to MDA-LDL levels, the MDA-LDL/LDL-C ratio was higher in patients with CAD compared with patients without CAD [20,24]. Our study suggested that in patients with ACS, higher MDA-LDL levels also reflected a higher MDA-LDL/LDL-C ratio, which could represent a stronger atherogenic state.

Our study also showed that the onset age of ACS was younger in the highest MDA-LDL group. This finding suggests that younger patients with ACS have poor lipid balance and strong oxidative stress, and these factors could contribute to their younger onset of ACS. Ogawa et al studied patients who underwent CAG, including CAD and normal coronary arteries [22]. These authors found that there was a negative correlation between MDA-LDL levels and age, similar to our study. However, Toshima et al reported that there was no significant correlation between oxidized LDL levels and age in patients with CAD [25]. Additionally, Holvoet et al reported that oxidized LDL and MDA-LDL levels were positively correlated with age in patients with ACS, stable angina pectoris, and heart transplant, as well as in controls [2]. Further studies are required to determine the correlation between MDA-LDL levels and age, especially in patients with ACS.

Our study showed that in patients with ACS, elevated MDA-LDL levels were able to predict future events of MACCE, especially revascularization after PCI. Few other studies have focused on the relation between MDA-LDL levels and prognosis of patients with CAD [7-8]. Ito et al reported that MDA-LDL levels were significantly associated with future cardiac events after PCI with drug-eluting stents in patients with stable angina pectoris under lipid-lowering therapy [7].

A recent study that used optical coherence tomography showed that MDA-LDL levels were correlated with the presence of thin-cap fibroatheromas in the culprit lesion [18]. Another report on integrated backscatter intravascular ultrasound showed that higher MDA-LDL levels suggested the presence of a plaque with greater lipid and lower fibrous content in culprit lesions [19]. Moreover, Sahara et al reported that soft plaques, namely lipid-rich plaques, detected on intravascular ultrasound were the strongest predictor of in-stent restenosis [26]. This was because soft plaques could be compressed more easily by stenting, but also caused proliferation of the neointima, and resulted in restenosis. Higher MDA-LDL levels in patients with ACS before PCI suggest the presence of soft and vulnerable plaques in the culprit lesion and/or the entire coronary artery. This could be a high-risk marker for predicting the future event of in-stent restenosis and progression of other lesions, which cause angina pectoris requiring revascularization. However, Naruko et al reported that although oxidized LDL levels at discharge were significantly correlated with in-stent restenosis at a 6-month follow-up in patients with acute myocardial infarction, oxidized LDL levels at admission did not show a significant correlation with future cardiac events [27]. Further studies are required to conclude whether MDA-LDL levels at admission or discharge are appropriate for predicting future cardiovascular events after PCI in patients with ACS.

There are several limitations to this study. First, this was a single-center, retrospective study and the sample size was relatively small. Second, most of the differences among the tertile groups occurred in soft endpoints, such as revascularization. In our study, body mass index, the ratio of smokers, and the prevalence of dyslipidemia were higher in patients with the highest tertile of MDA-LDL compared with other 2 groups. There is the possibility that higher MDA-LDL levels reflected accumulation of risk factors and that resulted in a higher prevalence of MACCE, including revascularization. However, MDA-LDL levels were a significant independent risk factor of MACCE after adjustment for these factors in this study. Finally, our study design precluded the investigation of a direct causal relationship. To determine this causal relationship between MDA-LDL levels and clinical events more directly, long-term interventional studies involving therapeutic agents that reduce MDA-LDL levels are warranted.

Conclusion

In patients with ACS, elevated serum MDA-LDL levels could be an important predictor of future cardiac events, especially in patients with ACS requiring revascularization after successful PCI.

Funding

This study was not supported by any grants and funds.

Disclosures

The authors declare that there is no conflict of interest.

References

1. Steinberg D. Low density lipoprotein oxidation and its pathobiological significance. J Biol Chem 1997;272:20963-6.
2. Holvoet P, Vanhaecke J, Janssens S, Werf F Van de, Collen D. Oxidized LDL and malondialdehyde-modified LDL in patients with acute coronary syndromes and stable coronary artery disease. Circulation 1998;98:1487-94.
3. Holvoet P, Mertens A, Verhamme P, Bogaerts K, Beyens G, Verhaeghe R, et al. Circulating Oxidized LDL Is a Useful Marker for Identifying Patients With Coronary Artery Disease. Arterioscler Thromb Vasc Biol 2001;21:844-8.
4. Inoue T, Uchida T, Kamishirado H, Takayanagi K, Hayashi T, Morooka S. Clinical significance of antibody against oxidized low density lipoprotein in patients with atherosclerotic coronary artery disease. J Am Coll Cardiol 2001;37:775-9.
5. Meisinger C, Baumert J, Khuseyinova N, Loewel H, Koenig W. Plasma oxidized low-density lipoprotein, a strong predictor for acute coronary heart disease events in apparently healthy, middle-aged men from the general population. Circulation 2005;112:651-7.
6. Amaki T, Suzuki T, Nakamura F, Hayashi D, Imai Y, Morita H, et al. Circulating malondialdehyde modified LDL is a biochemical risk marker for coronary artery disease. Heart 2004;90:1211-3.
7. Ito T, Fujita H, Tani T, Ohte N. Malondialdehyde-modified low-density lipoprotein is a predictor of cardiac events in patients with stable angina on lipid-lowering therapy after percutaneous coronary intervention using drug-eluting stent. Atherosclerosis 2015;239:311-7.
8. Shigematsu S, Takahashi N, Hara M, Yoshimatsu H, Saikawa T. Increased incidence of coronary in-stent restenosis in type 2 diabetic patients is related to elevated serum malondialdehyde-modified low-density lipoprotein. Circ J 2007;71:1697-702.
9. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD; Joint

ESC/ACCF/AHA/WHF Task Force for the Universal Definition of Myocardial Infarction, Katus HA, Lindahl B, Morrow DA, Clemmensen PM, Johanson P, Hod H, Underwood R, Bax JJ, Bonow RO, MS. Third Universal Definition of Myocardial Infarction. Circulation 2012;126:2020-35.

10. Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B, et al. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. Circulation 2011;124:e574-651.
11. Anderson JL, Adams CD, Antman EM, Bridges CR, Califf RM, Casey DE, et al. ACC/AHA 2007 Guidelines for the Management of Patients With Unstable Angina/Non–ST-Elevation Myocardial Infarction: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non–ST-Elevation Myocardial Infarction): Developed in Collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons: Endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine. Circulation 2007;116:e148-e304.
12. Antman EM, Hand M, Armstrong PW, Bates ER, Green LA, Halasyamani LK, et al. 2007 Focused update of the ACC/AHA 2004 guidelines for the management of patients with ST-elevation myocardial infarction: A report of the American College of Cardiology/American Heart Association task force on practice guidelines. Circulation 2008;117:296-329.
13. Kotani K, Maekawa M, Kanno T, Kondo A, Toda N, Manabe M. Distribution of immunoreactive malondialdehyde-modified low-density lipoprotein in human serum. Biochim Biophys Acta 1994;1215:121-5.

14. Kotani K, Caccavello R, Taniguchi N, Gugliucci A. Circulating soluble receptor for advanced glycation end products is inversely correlated to oxidized low-density lipoproteins in asymptomatic subjects. J Int Med Res 2012;40:1878-83.
15. Tonino PA, De Bruyne B, Pijls NH, Siebert U, Ikeno F, van' t Veer M, et al. Fractional Flow Reserve versus Angiography for Guiding Percutaneous Coronary Intervention. N Engl J Med 2009;360:213-24.
16. Holvoet P, Collen D, Werf F Van de. Malondialdehyde-modified LDL as a marker of acute coronary syndromes. JAMA 1999;281:1718-21.
17. Tajika K, Okamatsu K, Takano M, Inami S, Yamamoto M, Murakami D, et al. Malondialdehyde-modified low-density lipoprotein is a useful marker to identify patients with vulnerable plaque. Circ J 2012;76:2211-7.
18. Matsuo Y, Kubo T, Okumoto Y, Ishibashi K, Komukai K, Tanimoto T, et al. Circulating malondialdehyde-modified low-density lipoprotein levels are associated with the presence of thin-cap fibroatheromas determined by optical coherence tomography in coronary artery disease. Eur Heart J Cardiovasc Imaging 2013;14:43-50.
19. Ikenaga H, Kurisu S, Kono S, Sumimoto Y, Watanabe N, Shimonaga T, et al. Impact of Malondialdehyde-Modified Low-Density Lipoprotein on Tissue Characteristics in Patients With Stable Coronary Artery Disease – Integrated Backscatter-Intravascular Ultrasound Study –. Circ J 2016;80:2173-82.
20. Tanaga K, Bujo H, Inoue M, Mikami K, Kotani K, Takahashi K, et al. Increased circulating malondialdehyde-modified LDL levels in patients with coronary artery diseases and their association with peak sizes of LDL particles. Arterioscler Thromb Vasc Biol 2002;22:662-66.
21. Burgos Alves MI, Avilés Plaza F, Martínez-Tomás R, Sánchez-Campillo M, Larqué E, Pérez-Llamas F, et al. Oxidized LDL and its correlation with lipid profile and oxidative stress biomarkers in young healthy Spanish subjects. J Physiol Biochem 2010;66:221-7.
22. Ogawa K, Tanaka T, Nagoshi T, Sekiyama H, Arase S, Minai K, et al. Increase in the

oxidised low-density lipoprotein level by smoking and the possible inhibitory effect of statin therapy in patients with cardiovascular disease: a retrospective study. BMJ Open 2015;5:e005455.

23. Holvoet P, Keyzer D De, Jacobs DR. Oxidized LDL and metabolic syndrome. Futur Lipidol 2008;3:637-49.
24. Hiki M, Shimada K, Ohmura H, Kiyanagi T, Kume A, Sumiyoshi K, et al. Serum levels of remnant lipoprotein cholesterol and oxidized low-density lipoprotein in patients with coronary artery disease. J Cardiol 2009;53:108-16.
25. Toshima S, Hasegawa A, Kurabayashi M, Itabe H, Takano T, Sugano J, et al. Circulating oxidized low density lipoprotein levels. A biochemical risk marker for coronary heart disease. Arterioscler Thromb Vasc Biol 2000;20:2243-7.
26. Sahara M, Kirigaya H, Oikawa Y, Yajima J, Nagashima K, Hara H, et al. Soft plaque detected on intravascular ultrasound is the strongest predictor of in-stent restenosis: An intravascular ultrasound study. Eur Heart J 2004;25:2026-33.
27. Naruko T, Ueda M, Ehara S, Itoh A, Haze K, Shirai N, et al. Persistent high levels of plasma oxidized low-density lipoprotein after acute myocardial infarction predict stent restenosis. Arterioscler Thromb Vasc Biol 2006;26:877-83.

Figure legends

Figure 1. Flow chart showing selection of patients in main study.

ACS = acute coronary syndrome; CABG = coronary artery bypass grafting; MDA-LDL = malondialdehyde-modified low-density lipoprotein; PCI = percutaneous coronary intervention; SAP = stable angina pectoris.

Figure 2. Flow chart of patient follow-up in coronary angiography (main study).

ACS = acute coronary syndrome; PCI = percutaneous coronary intervention.

Figure 3. Kaplan-Meier analysis of cumulative event-free rates after PCI in patients with ACS, according to tertile value of serum MDA-LDL (A), total cholesterol (B), LDL-C (C), HDL-C (D), triglyceride (E) levels (main study).

ACS = acute coronary syndrome; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; MDA-LDL = malondialdehyde-modified low-density lipoprotein; PCI = percutaneous coronary intervention.

Online Figure 1. Kaplan-Meier analysis of cumulative event-free rates after PCI in patients with AMI, according to median of MDA-LDL (sub-study).

AMI = acute myocardial infarction; MDA-LDL = malondialdehyde-modified low-density lipoprotein; PCI = percutaneous coronary intervention.