

Impact of Low-Density Lipoprotein Cholesterol Levels at Acute Coronary Syndrome Admission on Long-Term Clinical Outcomes

Ryosuke Sato¹, Yasushi Matsuzawa^{1,2}, Tomohiro Yoshii¹, Eiichi Akiyama¹, Masaaki Konishi³, Hidefumi Nakahashi¹, Yugo Minamimoto¹, Yuichiro Kimura¹, Kozo Okada¹, Nobuhiko Maejima¹, Noriaki Iwahashi¹, Masami Kosuge¹, Toshiaki Ebina¹, Kazuo Kimura¹, Kouichi Tamura³ and Kiyoshi Hibi¹

¹Division of Cardiology, Yokohama City University Medical Center, Yokohama, Japan

²Department of Cardiovascular Medicine, Kumamoto University Hospital, Kumamoto, Japan

³Department of Medical Science and Cardiorenal Medicine, Yokohama City University, Graduate School of Medicine, Yokohama, Japan

Aim: Low-density lipoprotein cholesterol (LDL-C) level reduction is highly effective in preventing the occurrence of a cardiovascular event. Contrariwise, an inverse association exists between LDL-C levels and prognosis in some patients with cardiovascular diseases—the so-called “cholesterol paradox.” This study aimed to investigate whether the LDL-C level on admission affects the long-term prognosis in patients who develop acute coronary syndrome (ACS) and to examine factors associated with poor prognosis in patients with low LDL-C levels.

Methods: We enrolled 410 statin-naïve patients with ACS, whom we divided into low- and high-LDL-C groups based on an admission LDL-C cut-off (obtained from the Youden index) of 122 mg/dL. Endothelial function was assessed using the reactive hyperemia index 1 week after statin initiation. The primary composite endpoint included all-cause death, as well as myocardial infarction and ischemic stroke occurrences.

Results: During a median follow-up period of 6.1 years, 76 patients experienced the primary endpoint. Multivariate Cox regression analysis revealed that patients in the low LDL-C group had a 2.3-fold higher risk of experiencing the primary endpoint than those in the high LDL-C group (hazard ratio, 2.34; 95% confidence interval, 1.29–4.27; $p=0.005$). In the low LDL-C group, slow gait speed (frailty), elevated chronic-phase high-sensitivity C-reactive protein levels (chronic inflammation), and endothelial dysfunction were significantly associated with the primary endpoint.

Conclusions: Patients with low LDL-C levels at admission due to ACS had a significantly worse long-term prognosis than those with high LDL-C levels; frailty, chronic inflammation, and endothelial dysfunction were poor prognostic factors.

Key words: Cholesterol paradox, Low-density lipoprotein cholesterol, Acute coronary syndrome, Frailty, Residual inflammatory risk

Introduction

It is well established that dyslipidemia, especially an increase in low-density lipoprotein cholesterol (LDL-C) levels, is one of the most important risk factors for atherosclerotic cardiovascular diseases (ASCVDs). Numerous randomized clinical trials have clearly indicated that the lower the LDL-C level, the

lower the risk of future cardiovascular events¹⁻²; moreover, all major guidelines recommend an early, in-hospital initiation of strong statin treatment, particularly in the context of acute coronary syndrome (ACS)³⁻⁴. In contrast, some studies have shown an association between low LDL-C levels and short-term poor prognosis in patients with cardio-cerebrovascular diseases—the so-called “cholesterol paradox”⁵⁻⁶.

Address for correspondence: Yasushi Matsuzawa, Department of Cardiovascular Medicine, Kumamoto University Hospital, 1-1-1 Honjo, Chuo-ku, Kumamoto, 860-8556, Japan E-mail: matsuzawa-y@kumamoto-u.ac.jp

Received: May 16, 2023 Accepted for publication: August 21, 2023

Copyright©2024 Japan Atherosclerosis Society

This article is distributed under the terms of the latest version of CC BY-NC-SA defined by the Creative Commons Attribution License.

However, many of those studies have focused on all-cause mortality rather than cardiovascular events such as cardiovascular death or myocardial infarction, showing the “cholesterol survival paradox,” which has been speculated to be caused by malnutrition and other comorbidities such as cancer. Nevertheless, little is known about the pathogenesis underlying this paradox, and there is also a paucity of data regarding the impact of the cholesterol paradox on subsequent atherosclerotic events and long-term prognosis in patients with ACS.

Aim

This study aimed to investigate whether LDL-C levels on admission affect the long-term prognosis in patients who develop ACS with low LDL-C levels and to examine factors associated with poor prognosis in these patients.

Methods

Study Population

This is a retrospective observational study conducted at Yokohama City University Medical Center, Yokohama, Japan. Between June 2010 and November 2014, we enrolled patients who were hospitalized for ACS and participated in a study investigating the relationship between endothelial dysfunction and their prognosis⁷. ACS was defined as either or both the presence of anginal symptoms associated with an electrocardiographic ST-segment elevation or depression of at least 0.1 mV in two or more continuous leads and a rise in cardiac-specific troponin I level. All patients underwent either or both coronary angiography and computed tomography coronary angiography and were diagnosed with coronary artery diseases after hospitalization. We excluded patients who had no atherosclerotic coronary stenosis (>75% lumen stenosis), were taking statin therapy on admission, were on hemodialysis, did not start regular or strong statins (atorvastatin, pitavastatin, or rosuvastatin) before discharge, and had no available LDL-C data. Patients on hemodialysis were excluded because the arm with an arteriovenous shunt may influence a reactive hyperemic reaction during endothelial function assessment. Coronary artery revascularization was performed as needed, and Japanese guideline-based medical treatments were administered⁸. The patients were divided into low LDL-C (≤ 122 mg/dl) and high LDL-C groups, and the maximum Youden index in predicting the primary endpoint was used to determine the cut-off value (**Supplemental Fig. 1**). All patients were initiated on

statin therapy as soon as possible following admission. The study protocol was approved by the institutional review board of Yokohama City University Medical Center, and the need for written informed consent was waived by the institutional review board due to the retrospective nature of the study. The present study was conducted in accordance with the principles of the Declaration of Helsinki and the ethical standards of the responsible committee on human experimentation.

Clinical and Laboratory Measurement

Blood samples were obtained immediately on admission, and conventional glucose parameters (hemoglobin A1c and blood glucose) as well as LDL-C, high-density lipoprotein cholesterol, triglycerides, creatinine, B-type natriuretic peptide (BNP), and high-sensitivity C-reactive protein (hs-CRP) levels were evaluated. The estimated glomerular filtration rate (eGFR) was calculated using the prediction equation proposed by the Japanese Society of Nephrology, based on the Modification of Diet in Renal Disease Study⁹. Elevated inflammatory status was defined as an hs-CRP concentration of ≥ 0.2 mg/dL, which is commonly used¹⁰. We evaluated the nutritional status of the patients using the geriatric nutrition risk index (GNRI)¹¹ on admission, and malnutrition was defined as a GNRI of <92 , as previously reported¹². The left ventricular ejection fraction (LVEF) was assessed using echocardiography on admission. LDL-C levels and reductions at 1 month, 6 months, and 1 year after discharge were obtained from the electronic medical record with a margin of 3 months around each time point. Similarly, the inflammatory status in the chronic phase was assessed by the hs-CRP levels within 1–6 months after discharge. The LDL-C levels at 1 month, 6 months, and 1 year after discharge and hs-CRP levels in the chronic phase were available in 81.7% ($n=335$), 84.1% ($n=345$), 79.5% ($n=326$), and 97.3% ($n=399$) of patients, respectively.

Assessment of Frailty and Endothelial Function

Before discharge, all patients were enrolled in a cardiac rehabilitation program during their hospitalization in accordance with the Japanese Cardiovascular Society guidelines for the rehabilitation of patients with ACS⁸, as part of which their gait speed, one of the components defining frailty, was evaluated as a measure of frailty^{13, 14}. Patients were instructed to take a 200- or 500-m walk—at their usual pace without overexertion—in a wide hallway on a 50-m course during the daytime. Concomitantly, a trained physical therapist used a digital stopwatch to

measure the patient's gait speed. Participants who normally use canes and walkers in their daily lives were permitted to use them for the frailty evaluation. Data on gait speed was available in 83.9% of patients ($n=344$). Peripheral endothelial function was assessed by reactive hyperemia-peripheral arterial tonometry (RH-PAT)¹⁵⁻¹⁷ using EndoPAT2000 (Itamar Medical, Caesarea, Israel) just before discharge. Patients underwent RH-PAT in a fasting state, early in the morning, and prior to medication intake. RH-PAT data were automatically analyzed online in an operator-independent manner using the EndoPAT2000 software (Itamar Medical, Caesarea, Israel). The logarithmic value of the reactive hyperemia index was used in the abovementioned analyses, as previously described¹⁸.

Endpoints

The primary endpoint of this study was defined as a composite of all-cause death and the first episode(s) of nonfatal myocardial infarction and nonfatal ischemic stroke. The secondary endpoint was defined as a composite of all-cause death and the first episode(s) of either or all of the following: nonfatal myocardial infarction, nonfatal ischemic stroke, hospitalization for heart failure, and unplanned coronary revascularization. Patients were followed up in January 2020 by two interviewers using electronic medical records, telephone calls to them or their families, and direct consultation with their attending physicians. All medical records were independently reviewed by three cardiologists from the event committee to confirm the diagnosis. If the diagnosis differed among them, the differences were adjudicated. Nonfatal myocardial infarction was defined as an increase or decrease in cardiac biomarker levels with at least one value above the 99th percentile of the upper limit of the reference range and at least one of the following findings: ischemia, electrocardiographic changes (new ST-T changes, left bundle branch block, or pathological Q wave development), and imaging evidence of new viable myocardium loss or new regional wall motion abnormality. Nonfatal ischemic stroke was defined as the presence of a documented focal neurologic deficit and clinically relevant radiological evidence of brain infarction. Congestive heart failure was defined as a condition—the presence of typical heart failure symptoms, pulmonary edema, or congestion on chest radiography—that required intravenous drug administration.

Statistical Analysis

Statistical calculations were performed using JMP Pro® 15 (SAS Institute Inc., Cary, NC, USA).

Continuous variables with normal or skewed distributions were expressed as mean $\pm$ standard deviation or median [25th–75th percentile], respectively, whereas categorical variables were expressed as frequencies and percentages. Continuous variables were compared using the unpaired or paired Student *t*-test, Wilcoxon rank-sum test, Mann–Whitney *U* test, or one-way analyses of variance, as appropriate. Categorical variables were compared using the chi-square test. Survival analysis was performed using the Kaplan–Meier method and the log-rank test. Hazard ratios and 95% confidence intervals were analyzed using Cox proportional hazards regression models. The association between low LDL-C levels at admission due to ACS and the primary composite outcome was evaluated using four multivariate models: Model 1 (adjusted for age, sex, diabetes mellitus, myocardial infarction history, eGFR, and LVEF); Model 2 (adjusted for age, sex, cancer, chronic-phase inflammation, malnutrition, and gait speed); Model 3 (adjusted for propensity score calculated using logistic regression analysis with a low or high LDL-C group as a dependent variable and all variables significantly associated with the primary composite outcome in the univariate analysis (age, diabetes mellitus, eGFR on admission, triglycerides on admission, BNP on admission, hs-CRP ≥ 0.2 mg/dL in the chronic phase, GNRI <92 , LVEF on admission, multivessel disease, strong statin use at discharge, gait speed, and logarithmic value of reactive hyperemia index) as independent variables.), respectively. A *p*-value of <0.05 was considered statistically significant.

Results

Patient Characteristics

We enrolled 410 statin-naïve patients with ACS, all of whom received statin therapy during the study period (**Fig. 1**). The patients were divided into low and high LDL-C groups using the LDL-C cut-off value of 122 mg/dl on admission. During the follow-up period, there were 45 deaths (28, 10, 3, and 4 were deaths from cardiovascular diseases, cancer, pneumonia, and other causes, respectively). Cardiovascular deaths included 9 sudden deaths, 8 heart failure deaths, 2 stroke deaths, and 9 other cardiovascular causes. Moreover, 16, 19, 20, and 37 patients had nonfatal myocardial infarction, nonfatal ischemic stroke, heart failure hospitalization, and unplanned coronary revascularization, respectively. The primary and secondary endpoints were experienced by 76 and 115 patients, respectively. The

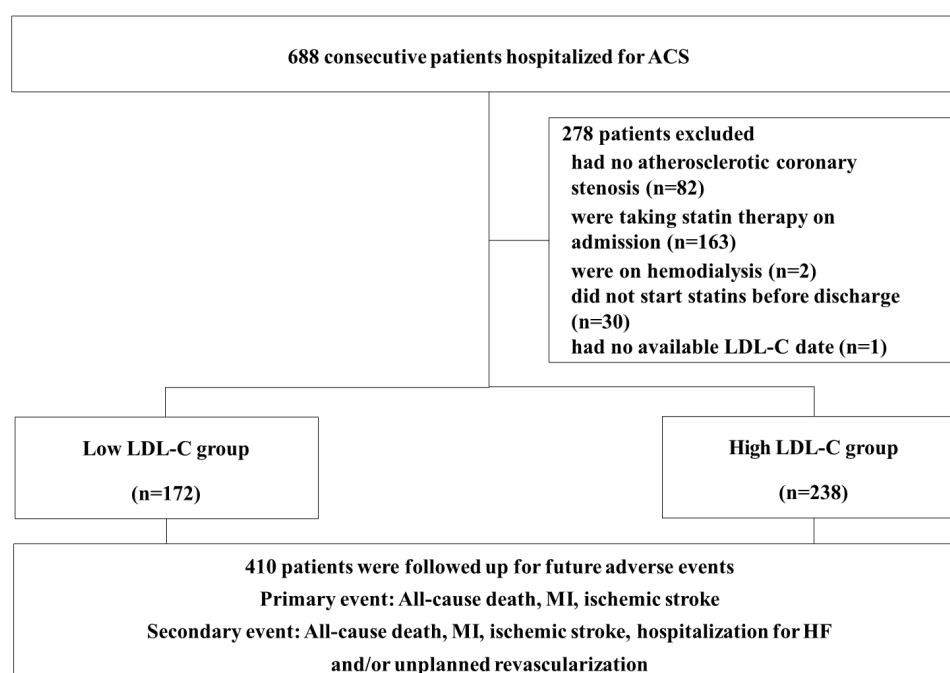


Fig. 1. Study flow chart

ACS, acute coronary syndrome; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; HF, heart failure

patients in the low LDL-C group were older and had a higher prevalence of diabetes mellitus, lower levels of eGFR and HDL-C, higher levels of BNP, and a lower ST—segment elevation myocardial infarction (STEMI) proportion compared with those in the high LDL-C group. Strong statins were less frequently administered in the low than in the high LDL-C group ([Table 1](#)).

Changes in LDL-C Levels among the Low and High LDL-C Groups

The reduction in LDL-C levels was evident after 1 month of statin use and was maintained until 1 year after discharge in both the low and high LDL-C groups ([Fig. 2A](#)). LDL-C levels were significantly lower throughout the year after enrollment in the low LDL-C group than in the high LDL-C group. In contrast, the percent reduction in LDL-C levels from baseline was consistently and significantly greater in the high LDL-C group than in the low LDL-C group at any observational point ([Fig. 2B](#)).

Impact of Low LDL-C Levels on Long-Term Outcomes

Kaplan–Meier analysis over a median follow-up period of 6.1 years revealed a significantly lower event-free rate for the primary and secondary composite outcomes in the low than in the high LDL-C group

([Fig. 3A and 3B](#)). The abovementioned finding was significant, albeit observed only in patients taking strong statins ([Supplemental Fig. 2A and 2B](#)). There were significantly higher rates of all-cause death (18.0% vs. 5.9%, $p=0.0002$), cardiovascular death (9.9% vs. 4.6%, $p=0.03$), noncardiovascular death (8.1% vs. 1.3%, $p=0.0008$), and nonfatal myocardial infarction (6.4% vs. 2.1%, $p=0.02$) in the low LDL-C group than in the high LDL-C group ([Table 2](#)). Among cardiovascular deaths, there were significantly higher rates of heart failure deaths in the low LDL-C group than those in the high LDL-C group (3.5% vs. 0.8%, $p=0.04$); none of the other causes showed significant differences between the two groups (sudden death: 2.3% vs. 2.1%, $p=0.77$; stroke: 0.6% vs. 0.4%, $p=0.79$; other cardiovascular causes: 3.5% vs. 1.3%, $p=0.12$). The rate of hospitalization for heart failure was not significantly different between the two groups but tended to be higher in the low than in the high LDL-C group (7.0% vs. 3.4%, $p=0.08$).

Factors Associated with the Primary Composite Outcome

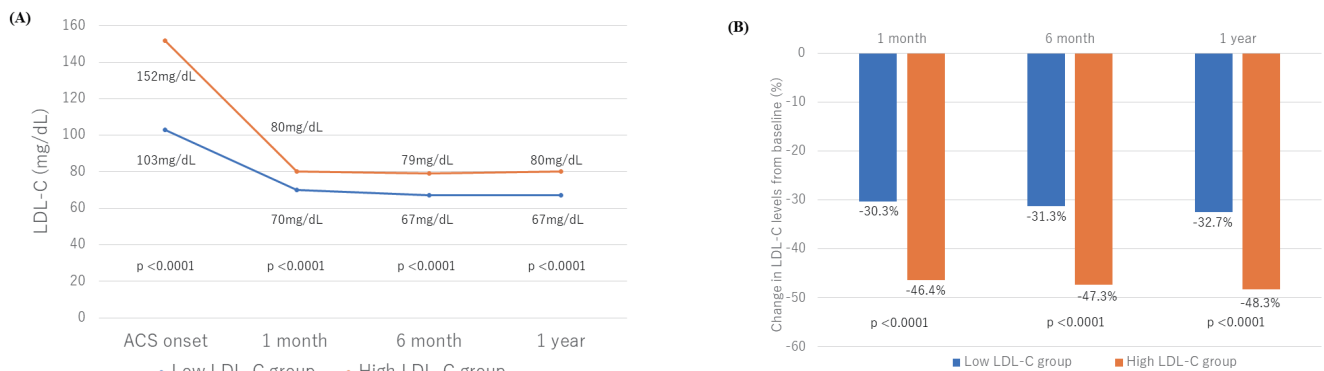
Univariate Cox regression analysis revealed that the following factors were associated with the primary composite outcome: older age, diabetes mellitus, eGFR, triglyceride levels, BNP levels, hs-CRP levels in the chronic phase, GNRI <92, LVEF, multivessel

Table 1. Baseline characteristics of patients in the low and high LDL-C groups

	Overall (<i>n</i> = 410)	Low LDL-C group (<i>n</i> = 172)	High LDL-C group (<i>n</i> = 238)	<i>p</i> -value
Age, years	65 ± 13	68 ± 12	63 ± 12	<0.0001
Male sex, <i>n</i> (%)	337 (82.2)	147 (85.5)	190 (79.8)	0.14
Body mass index, kg/m ²	24.0 ± 3.5	23.9 ± 3.7	24.0 ± 3.4	0.56
Hypertension, <i>n</i> (%)	247 (60.2)	112 (65.1)	135 (56.7)	0.09
Diabetes mellitus, <i>n</i> (%)	122 (29.8)	66 (38.4)	56 (23.5)	0.001
Current smoker, <i>n</i> (%)	201 (49.1)	82 (48.0)	119 (50.0)	0.68
History of MI, <i>n</i> (%)	21 (5.1)	6 (3.5)	15 (6.3)	0.20
With cancer, <i>n</i> (%)	17 (4.2)	8 (4.7)	9 (3.8)	0.66
eGFR on admission, mg/dL	68.0 [55.6-80.4]	66.3 [51.6-75.1]	70.6 [57.4-83.5]	0.004
HDL-C on admission, mg/dL	44 [38-52]	42 [37-51]	45 [39-53]	0.02
LDL-C on admission, mg/dL	130 [108-156]	103 [92-113]	152 [137-171]	<0.0001
TG on admission, mg/dL	121 [81-186]	119 [76-192]	122 [85-183]	0.96
BNP on admission, pg/mL	49 [21-120]	57 [25-151]	44 [17-108]	0.03
hs-CRP ≥ 0.2 mg/dL on admission, <i>n</i> (%)	191 (46.7)	79 (45.9)	112 (47.3)	0.79
hs-CRP ≥ 0.2 mg/dL in the chronic phase, <i>n</i> (%) (<i>n</i> = 399)	90 (22.6)	43 (25.4)	47 (20.4)	0.24
GNRI < 92, <i>n</i> (%)	33 (8.1)	17 (9.9)	16 (6.8)	0.24
LVEF on admission, %	50 ± 11	50 ± 12	50 ± 11	0.84
STEMI, <i>n</i> (%)	301 (73.4)	117 (68.0)	184 (77.3)	0.04
Multivessel disease, <i>n</i> (%)	182 (44.4)	82 (47.7)	100 (42.0)	0.26
Medication at discharge				
Aspirin, <i>n</i> (%)	406 (99.0)	170 (98.8)	236 (99.0)	0.74
Beta blocker, <i>n</i> (%)	252 (61.6)	102 (59.7)	150 (63.0)	0.49
ACE-I or ARB, <i>n</i> (%)	333 (81.2)	137 (79.7)	196 (82.4)	0.49
Strong statin, <i>n</i> (%)	382 (93.2)	146 (84.9)	236 (99.2)	<0.0001
Gait speed, m/s (<i>n</i> = 344)	0.85 ± 0.23	0.84 ± 0.22	0.86 ± 0.23	0.45
Ln RHI	0.59 ± 0.26	0.57 ± 0.25	0.61 ± 0.26	0.12

Variables are expressed as numbers (percentages), mean ± SD, or median [25th-75th percentile].

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BNP, B-type natriuretic peptide; eGFR, estimated glomerular filtration rate; GNRI, geriatric nutritional risk index; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; Ln RHI, logarithmic value of reactive hyperemia index; LVEF, left ventricular ejection fraction; MI, myocardial infarction; SD, standard deviation; STEMI, ST-segment elevation myocardial infarction; TG, triglycerides.

**Fig. 2.** Changes in LDL-C levels among low and high LDL-C group patients

(A) LDL-C levels over time, (B) Percent reduction in LDL-C levels

ACS, acute coronary syndrome; LDL-C, low-density lipoprotein cholesterol.

The reduction in LDL-C levels was maintained until 1 year after discharge in both the low and high LDL-C groups. The percent reduction in LDL-C levels from baseline was consistently and significantly greater in the high than in the low LDL-C group at any observational point.

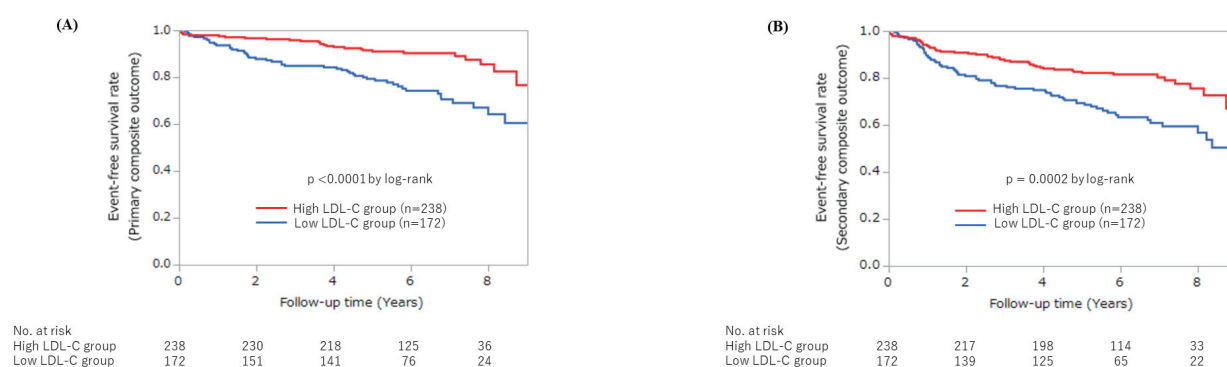


Fig. 3. Kaplan–Meier curves of event-free cumulative rate for primary and secondary composite outcomes in the low and high LDL-C groups

(A) Primary composite outcome, (B) Secondary composite outcome
 LDL-C, low-density lipoprotein cholesterol.

Kaplan–Meier analysis revealed a significantly lower event-free rate for the primary and secondary composite outcomes in the low than in the high LDL-C group.

Table 2. Primary and secondary composite outcomes after ACS in patients with low and high LDL-C levels

	Overall (n = 410)	Low LDL-C group (n = 172)	High LDL-C group (n = 238)	p-value
Primary composite outcome: all-cause death, nonfatal MI, or nonfatal ischemic stroke, n (%)	76 (18.5)	49 (28.5)	27 (11.3)	<0.0001
Secondary composite outcome: all-cause death, nonfatal MI, nonfatal ischemic stroke, hospitalization for HF, or unplanned revascularization, n (%)	115 (28.0)	66 (38.4)	49 (20.6)	0.0002
All-cause death, n (%)	45 (11.0)	31 (18.0)	14 (5.9)	0.0002
Cardiovascular death, n (%)	28 (6.8)	17 (9.9)	11 (4.6)	0.03
Non-cardiovascular death, n (%)	17 (4.1)	14 (8.1)	3 (1.3)	0.0008
Nonfatal MI, n (%)	16 (3.9)	11 (6.4)	5 (2.1)	0.02
Nonfatal ischemic stroke, n (%)	19 (4.6)	8 (4.7)	11 (4.6)	0.93
Hospitalization for HF, n (%)	20 (4.9)	12 (7.0)	8 (3.4)	0.08
Unplanned revascularization, n (%)	37 (9.0)	18 (10.5)	19 (8.0)	0.33

Data were expressed as counts (percentages). Significance was assessed by the log-rank test. ACS, acute coronary syndrome; HF, heart failure; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction

disease, strong statin use at discharge, gait speed, RHI, and low LDL-C levels on admission (**Supplemental Table 1**). The multivariate models revealed that a low LDL-C level at admission due to ACS was significantly and independently associated with the primary composite outcome (**Table 3**).

Risk Factors of Cardiovascular Events in the Low LDL-C Group

During the follow-up period, the primary endpoint occurred in 49 patients in the low LDL-C group. Baseline characteristics of patients in the low LDL-C group with or without a primary outcome are shown in **Supplemental Table 2**. The prevalence of established prognostic factors for coronary heart

disease (sex, myocardial infarction history, renal function, diabetes mellitus, and LVEF) and the proportion of patients undergoing strong statin therapy at discharge were comparable between patients in the low LDL-C group with and without a primary outcome. Univariate analysis revealed that older age, elevated levels of chronic-phase inflammatory response markers, slow gait speed, and endothelial dysfunction were significantly associated with the primary outcome in the low LDL-C group (**Supplemental Table 3**). In contrast, in the high LDL-C group, endothelial dysfunction was similarly a significant predictor of primary outcome, while chronic-phase inflammation and slow gait speed were not associated with primary outcome occurrence (**Supplemental Table 4**).

Table 3. Multivariate Cox proportional hazards analysis for the primary composite outcomes

	Primary composite outcome		
	HR	95%-CI	p-value
Model 1			
Adjusted for age, sex, DM, history of MI, eGFR, LVEF	1.94	1.16-3.22	0.01
Model 2			
Adjusted for age, sex, cancer, inflammation, malnutrition, gait speed	2.13	1.23-3.70	0.007
Model 3			
Adjusted for propensity score	2.34	1.29-4.27	0.005

The propensity score was calculated using logistic regression analysis with a low or high LDL-C group as a dependent variable and all variables significantly associated with the primary composite outcome in the univariate analysis (age, DM, eGFR on admission, TG on admission, BNP on admission, hs-CRP ≥ 0.2 mg/dL in the chronic phase, GNRI < 92 , LVEF on admission, multivessel disease, strong statin use at discharge, gait speed, and Ln RHI) as independent variables. BNP, B-type natriuretic peptide; CI, confidence interval; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; GNRI, geriatric nutrition risk index; HR, hazard ratio; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; Ln RHI, logarithmic value of reactive hyperemia index; LVEF, left ventricular ejection fraction; TG, triglycerides.

Discussion

Our study had two main findings. First, lower LDL-C levels at admission due to ACS were significantly associated with worse long-term prognosis, particularly with cardiovascular and noncardiovascular death and myocardial infarction, and this association was significant even after adjustment for clinically important and associated variables, traditional coronary artery disease risk factors, and several factors involved in lipid metabolism. Second, in the low LDL-C group, persistent inflammatory response, slow gait speed, and endothelial dysfunction were significantly associated with primary outcome occurrence. The present study suggests the necessity of applying interventions targeting chronic inflammation and frailty, in addition to guideline-recommended therapies (including cholesterol-lowering therapy), to improve the prognosis of patients who develop ACS with low LDL-C levels (Fig. 4).

Prognostic Impact of LDL-C Levels at ACS Admission

Aggressive LDL-C-lowering therapy with statins, ezetimibe, and proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors is an established treatment option for patients with ASCVDs¹⁹⁻²¹. In the present study, LDL-C levels in the chronic phase and an absolute reduction in LDL-C levels also tended to ameliorate the prognosis (Supplemental Table 1), thereby demonstrating the benefit of lipid-lowering statin therapy. However, some previous studies have demonstrated that higher LDL-C levels at the onset of cardio-cerebrovascular diseases are associated with better clinical outcomes⁵⁻⁶. Consistent with these

findings, the present study found significantly higher primary outcome rates in patients in the low than in the high LDL-C group. Similarly, Cho *et al.* recently showed that a baseline LDL-C level below 70 mg/dl was significantly associated with an increased subsequent cardiovascular event in patients with acute myocardial infarction²², while our present study is the first to extend their finding to patients with ACS and to demonstrate that lower LDL-C levels at admission due to ACS were associated with primary outcome occurrence even after adjusting for classical coronary artery disease risk factors, as well as nutritional status, cancer, frailty, and chronic inflammation. Aggressive lipid-lowering strategies with statins have an undeniable benefit; nonetheless, further addressing residual risk may be required for patients who develop ACS with low LDL-C levels.

Potential Mechanisms of the Cholesterol Paradox

Consistent evidence has shown that statin use reduces cardiovascular event occurrence in both the primary and secondary prevention settings, although up to 40% of patients experience life-threatening subsequent cardiovascular events despite control of LDL-C levels below the currently recommended targets²³. Recently, atherogenic dyslipidemia, inflammation, and frailty have received sufficient attention as residual risk factors for cardiovascular disease²⁴⁻²⁵. In the Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk and the Studies of PCSK9 Inhibition and the Reduction of Vascular Events trials, a persistently high hs-CRP level remained an unabated predictor of cardiovascular risk, despite extremely low LDL-C levels¹⁹⁻²⁰. Based on the abovementioned findings, Everett *et al.* proposed the need for

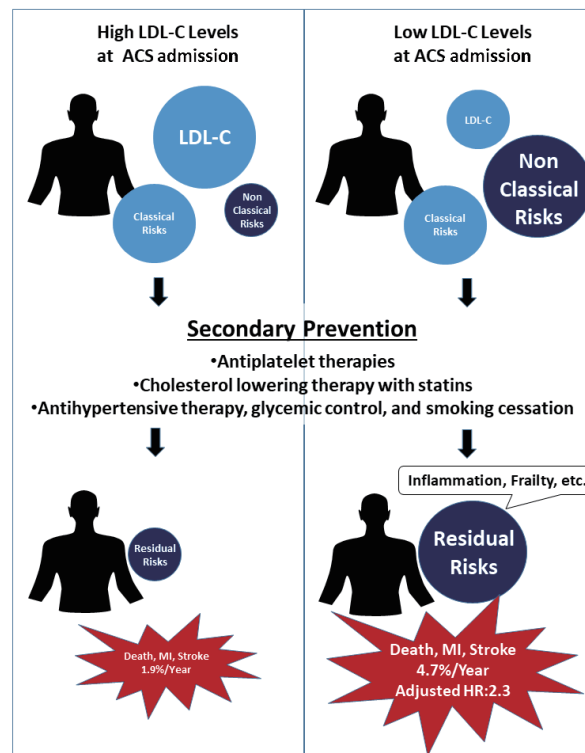


Fig. 4. Residual risk in secondary prevention according to LDL-C levels at ACS admission

ACS, acute coronary syndrome; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction.

Irrespective of the adjusted models used, the future risk of death, myocardial infarction, and stroke is two times higher in patients with low than with high LDL-C levels at ACS admission. In addition to LDL-C-lowering therapy, therapies targeting personal residual risk factors such as chronic inflammation, frailty, and atherogenic dyslipidemia may be needed to improve the prognosis of patients who develop ACS with low LDL-C levels.

interventions in the “residual inflammatory risk” of recurrent ischemic heart disease in addition to aggressive lipid-lowering therapy²⁶). In addition, Ridker *et al.* recently suggested that an anti-inflammatory therapy targeting interleukin-6—a central pro-inflammatory cytokine—could be a new therapeutic strategy for patients with ACS and chronic atherosclerosis²⁷). Furthermore, we previously reported that frailty, assessed by slow gait speed and low skeletal muscle mass, was significantly and independently associated with an increased risk of future cardiovascular events in patients with STEMI^{13, 28}). Comparably, the present study observed that slow gait speed and chronic inflammation are significantly associated with subsequent cardiovascular events in patients in the low LDL-C group (**Supplemental Table 3**). Also, while both groups showed a comparable LVEF, the low LDL-C group was older, had a higher prevalence of diabetes, and had worse kidney function than the high LDL-C group (**Table 1**), which all contribute to exacerbating coronary atherosclerosis and heart failure. Furthermore, although LDL-C levels in the chronic phase were

significantly lower in the low LDL-C group than in the high LDL-C group, the use of strong statins in the low LDL-C group was significantly lower, with its use being significantly associated with a better prognosis (**Table 1, Supplemental Table 1**). Strong statins have also been reported to induce a significant regression of coronary plaque volume in patients with ACS independent of LDL-C levels after statin therapy compared with standard statins²⁹). Taken together, the pleiotropic effect of strong statins beyond their lowering LDL-C levels might have partially influenced the prognosis in the low LDL-C group.

Meanwhile, in the low LDL-C group, patients with primary outcomes were significantly older, had higher levels of BNP and systemic inflammation in the chronic phase, and had worse endothelial function than those without primary outcomes (**Supplemental Table 2**). Chronic inflammation promotes coronary atherosclerosis and myocardial dysfunction or remodeling while causing physical frailty from skeletal muscle wasting³⁰⁻³¹). Endothelial dysfunction is a surrogate marker of cardiovascular disease and is also reported to be associated with physical frailty and

sarcopenia³²). Furthermore, frailty is common in both heart failure with reduced ejection fraction and heart failure with preserved ejection fraction and is associated with a high risk of adverse outcomes, irrespective of LVEF levels³³). Therefore, it could be inferred that patients who developed primary outcomes in the low LDL-C group had comparable LVEF as those without primary outcomes but were more complicated by frailty from chronic inflammation, endothelial dysfunction, and a predisposition to heart failure as well as aging.

Although the present findings do not shed light on the mechanism of the cholesterol paradox, the prognosis of patients with low LDL-C levels who developed ACS may involve frailty, chronic inflammation, endothelial dysfunction, and the pleiotropic effect of strong statins, as well as the traditional risks of atherosclerotic disease.

Clinical Implication

Previous studies have reported that endothelial dysfunction is associated with aging, inflammation, frailty, diabetes mellitus, and kidney dysfunction, indicating that endothelial dysfunction is a surrogate marker of cardiovascular event occurrence³⁴⁻³⁷). More recently, we demonstrated that endothelial dysfunction predicts subsequent major cardiovascular and bleeding events in patients with ACS⁷). In the present study, endothelial dysfunction was also associated with adverse cardiovascular event occurrence in both low and high LDL-C groups, while chronic inflammation and frailty were associated with prognosis only in the low LDL-C group. On the other hand, diabetes mellitus and renal dysfunction were predictors of adverse outcomes only in the high LDL-C group, suggesting that the underlying pathologies causing endothelial damage differ between the two groups.

Recently, the Canakinumab Anti-Inflammatory Thrombosis Outcomes Study trial involving stable patients with previous myocardial infarction showed that canakinumab, a therapeutic monoclonal antibody targeting interleukin-1 β , significantly reduced the cardiovascular event recurrence rate³⁸). Moreover, the Colchicine Cardiovascular Outcomes Trial revealed that low-dose colchicine reduces the risk of ischemic cardiovascular events among patients with recent myocardial infarction³⁹). Although not a few anti-inflammatory strategies have failed⁴⁰⁻⁴¹), the results of these two trials support the potential benefits of anti-inflammatory therapy after myocardial infarction. On the other hand, the efficacy of comprehensive cardiac rehabilitation in ASCVD prevention is well established⁴²), with some evidence indicating that cardiac rehabilitation programs may also improve

systemic inflammatory response and reverse frailty⁴³⁻⁴⁴). Taken together, the combination strategies of specific anti-inflammatory therapies and cardiac rehabilitation might improve clinical outcomes in patients who develop ACS with low LDL-C levels.

Study Limitations

The present study has several limitations. First, this was a retrospective, single-center study with a relatively small sample size, as it failed to include enough important groups with potentially poor outcomes for ACS, such as women, the elderly, and diabetic patients. In addition, due to the retrospective study design, we could not control for adherence to medication, including statins, or events such as cancer development during the follow-up period. The findings require confirmation using large-scale, prospective studies with predefined endpoints. Second, we used the cut-off value for LDL-C obtained from the Youden index, which predicts the primary endpoint, lowering the external validity of our findings. Third, the possible associations of frailty with muscle mass, social activities, mental state, and hormonal changes, as well as their impact on prognosis in patients with ACS, remain unclear. Indeed, frailty includes various conditions such as loss of muscle mass, social isolation, mental disorders, and testosterone insufficiency. Fourth, we did not routinely measure atherogenic lipoprotein levels and remnants. Recently, the Atherosclerosis Risk in Communities and the Treating to New Targets studies have demonstrated that atherogenic lipoproteins (such as lipoprotein (a), small dense LDL, remnants of very low-density lipoprotein, and chylomicrons) are risk factors for cardiovascular disease independent of LDL-C levels⁴⁵⁻⁴⁶). Therefore, the possible associations of the abovementioned factors with the cholesterol paradox in patients with ACS should be sufficiently investigated in the future. Fifth, blood samples were obtained at ACS admission; thus, the impact of decreasing cholesterol levels during the acute phase of ACS as shown in previous studies⁴⁷⁻⁴⁸) could not be considered. Sixth, there was no available data on lipid-lowering drugs other than statins, such as PCSK9 inhibitors and ezetimibe. Lastly, our study did not clarify whether chronic inflammation and frailty could be therapeutic targets to improve long-term clinical outcomes in patients with low LDL-C levels who developed ACS.

Conclusions

Low LDL-C levels at admission due to ACS were significantly and independently associated with a poor

prognosis after ACS. Frailty, chronic inflammation, and endothelial dysfunction were significantly associated with a worse prognosis in patients with low LDL-C levels at admission due to ACS. Further studies are needed to investigate whether therapies targeting inflammation, frailty, and endothelial dysfunction improve the outcomes of patients with low LDL-C levels at admission due to ACS.

Conflict of Interest:

KT received personal fees from Astrazenrca Novartis, AstraZeneca, Ono, Daiichi-Sankyo, Takeda, Otsuka, Bayer, Kyowa-Kirin, grants from Otsuka, Takeda, Daiichi-Sankyo, Bayer. The other authors report no conflicts of interest.

Acknowledgements

None.

Notice of Grant Support:

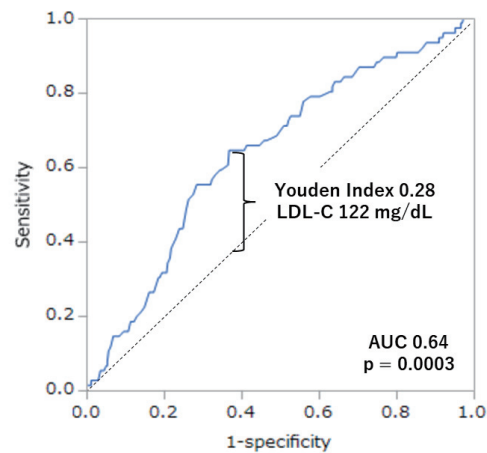
None.

References

- 1) Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, Bhala N, Peto R, Barnes EH, Keech A, Simes J and Collins R: Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet* (London, England), 2010; 376: 1670-1681
- 2) Boekholdt SM, Hovingh GK, Mora S, Arsenault BJ, Amarencu P, Pedersen TR, LaRosa JC, Waters DD, DeMicco DA, Simes RJ, Keech AC, Colquhoun D, Hitman GA, Betteridge DJ, Clearfield MB, Downs JR, Colhoun HM, Gotto AM, Jr., Ridker PM, Grundy SM and Kastelein JJ: Very low levels of atherogenic lipoproteins and the risk for cardiovascular events: a meta-analysis of statin trials. *J Am Coll Cardiol*, 2014; 64: 485-494
- 3) Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, Braun LT, de Ferranti S, Faiella-Tommasino J, Forman DE, Goldberg R, Heidenreich PA, Hlatky MA, Jones DW, Lloyd-Jones D, Lopez-Pajares N, Ndumele CE, Orringer CE, Peralta CA, Saseen JJ, Smith SC, Jr., Sperling L, Virani SS and Yeboah J: 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*, 2019; 139: e1082-e1143
- 4) Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, Chapman MJ, De Backer GG, Delgado V, Ference BA, Graham IM, Halliday A, Landmesser U, Mihaylova B, Pedersen TR, Riccardi G, Richter DJ, Sabatine MS, Taskinen MR, Tokgozoglu L and Wiklund O: 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J*, 2020; 41: 111-188
- 5) Al-Mallah MH, Hatahet H, Cavalcante JL and Khanal S: Low admission LDL-cholesterol is associated with increased 3-year all-cause mortality in patients with non ST segment elevation myocardial infarction. *Cardiology journal*, 2009; 16: 227-233
- 6) Cho KH, Jeong MH, Ahn Y, Kim YJ, Chae SC, Hong TJ, Seong IW, Chae JK, Kim CJ, Cho MC, Seung KB and Park SJ: Low-density lipoprotein cholesterol level in patients with acute myocardial infarction having percutaneous coronary intervention (the cholesterol paradox). *Am J Cardiol*, 2010; 106: 1061-1068
- 7) Yoshii T, Matsuzawa Y, Kato S, Sato R, Hanajima Y, Kikuchi S, Nakahashi H, Konishi M, Akiyama E, Minamimoto Y, Kimura Y, Okada K, Maejima N, Iwahashi N, Ebina T, Hibi K, Kosuge M, Misumi T, Tamura K and Kimura K: Endothelial dysfunction predicts bleeding and cardiovascular death in acute coronary syndrome. *Int J Cardiol*, 2023;
- 8) Kimura K, Kimura T, Ishihara M, Nakagawa Y, Nakao K, Miyauchi K, Sakamoto T, Tsujita K, Hagiwara N, Miyazaki S, Aki J, Arai H, Ishii H, Origuchi H, Shimizu W, Takemura H, Tahara Y, Morino Y, Iino K, Itoh T, Iwanaga Y, Uchida K, Endo H, Kongoji K, Sakamoto K, Shiomi H, Shimohama T, Suzuki A, Takahashi J, Takeuchi I, Tanaka A, Tamura T, Nakashima T, Noguchi T, Fukamachi D, Mizuno T, Yamaguchi J, Yodogawa K, Kosuge M, Kohsaka S, Yoshino H, Yasuda S, Shimokawa H, Hirayama A, Akasaka T, Haze K, Ogawa H, Tsutsui H and Yamazaki T: JCS 2018 Guideline on Diagnosis and Treatment of Acute Coronary Syndrome. *Circ J*, 2019; 83: 1085-1196
- 9) Imai E, Matsuo S, Makino H, Watanabe T, Akizawa T, Nitta K, Iimuro S, Ohashi Y and Hishida A: Chronic Kidney Disease Japan Cohort (CKD-JAC) study: design and methods. *Hypertension research: official journal of the Japanese Society of Hypertension*, 2008; 31: 1101-1107
- 10) Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM, Jr., Kastelein JJ, Koenig W, Libby P, Lorenzatti AJ, MacFadyen JG, Nordestgaard BG, Shepherd J, Willerson JT and Glynn RJ: Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *The New England journal of medicine*, 2008; 359: 2195-2207
- 11) Bouillanne O, Morineau G, Dupont C, Coulombel I, Vincent JP, Nicolis I, Benazeth S, Cynober L and Aussel C: Geriatric Nutritional Risk Index: a new index for evaluating at-risk elderly medical patients. *The American journal of clinical nutrition*, 2005; 82: 777-783
- 12) Nishi I, Seo Y, Hamada-Harimura Y, Yamamoto M, Ishizu T, Sugano A, Sato K, Sai S, Obara K, Suzuki S, Koike A, Aonuma K and Ieda M: Geriatric nutritional risk index predicts all-cause deaths in heart failure with preserved ejection fraction. *ESC heart failure*, 2019; 6: 396-405
- 13) Matsuzawa Y, Konishi M, Akiyama E, Suzuki H, Nakayama N, Kiyokuni M, Sumita S, Ebina T, Kosuge M,

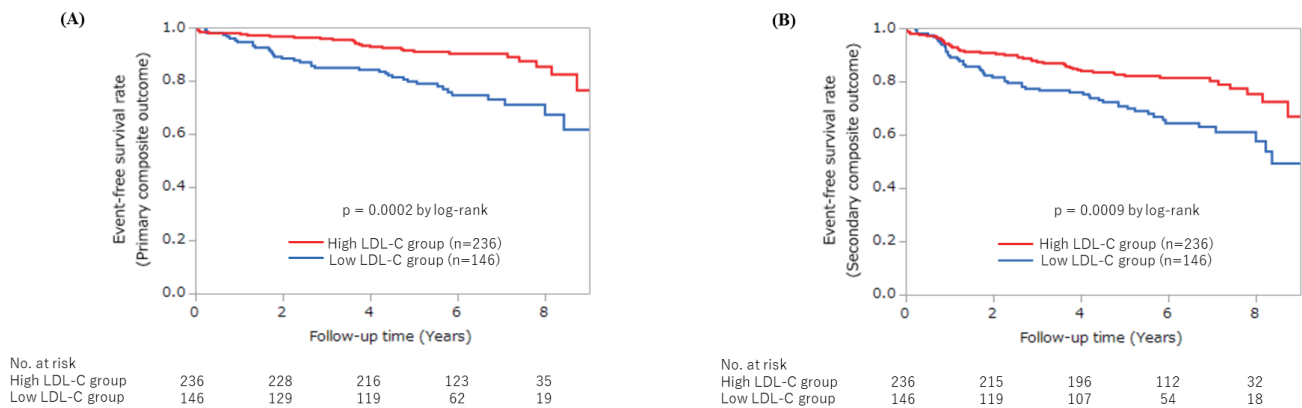
- Hibi K, Tsukahara K, Iwahashi N, Endo M, Maejima N, Saka K, Hashiba K, Okada K, Taguri M, Morita S, Sugiyama S, Ogawa H, Sashika H, Umemura S and Kimura K: Association between gait speed as a measure of frailty and risk of cardiovascular events after myocardial infarction. *J Am Coll Cardiol*, 2013; 61: 1964-1972
- 14) Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, Seeman T, Tracy R, Kop WJ, Burke G and McBurnie MA: Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci*, 2001; 56: M146-156
 - 15) Kuvin JT, Patel AR, Sliney KA, Pandian NG, Sheffy J, Schnall RP, Karas RH and Udelson JE: Assessment of peripheral vascular endothelial function with finger arterial pulse wave amplitude. *American heart journal*, 2003; 146: 168-174
 - 16) Matsuzawa Y, Sugiyama S, Sumida H, Sugamura K, Nozaki T, Ohba K, Matsubara J, Kurokawa H, Fujisue K, Konishi M, Akiyama E, Suzuki H, Nagayoshi Y, Yamamuro M, Sakamoto K, Iwashita S, Jinnouchi H, Taguri M, Morita S, Matsui K, Kimura K, Umemura S and Ogawa H: Peripheral endothelial function and cardiovascular events in high-risk patients. *J Am Heart Assoc*, 2013; 2: e000426
 - 17) Matsuzawa Y, Li J, Aoki T, Guddeti RR, Kwon TG, Cilluffo R, Widmer RJ, Gulati R, Lennon RJ, Lerman LO and Lerman A: Predictive value of endothelial function by noninvasive peripheral arterial tonometry for coronary artery disease. *Coronary artery disease*, 2015; 26: 231-238
 - 18) Matsuzawa Y, Sugiyama S, Sugamura K, Nozaki T, Ohba K, Konishi M, Matsubara J, Sumida H, Kaikita K, Kojima S, Nagayoshi Y, Yamamuro M, Izumiya Y, Iwashita S, Matsui K, Jinnouchi H, Kimura K, Umemura S and Ogawa H: Digital assessment of endothelial function and ischemic heart disease in women. *J Am Coll Cardiol*, 2010; 55: 1688-1696
 - 19) Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, Kuder JF, Wang H, Liu T, Wasserman SM, Sever PS and Pedersen TR: Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. *The New England journal of medicine*, 2017; 376: 1713-1722
 - 20) Ridker PM, Revkin J, Amarenco P, Brunell R, Curto M, Civeira F, Flather M, Glynn RJ, Gregoire J, Jukema JW, Karpov Y, Kastelein JJP, Koenig W, Lorenzatti A, Manga P, Masiukiewicz U, Miller M, Mosterd A, Murin J, Nicolau JC, Nissen S, Ponikowski P, Santos RD, Schwartz PF, Soran H, White H, Wright RS, Vrablik M, Yunis C, Shear CL and Tardif JC: Cardiovascular Efficacy and Safety of Bococizumab in High-Risk Patients. *The New England journal of medicine*, 2017; 376: 1527-1539
 - 21) Schwartz GG, Steg PG, Szarek M, Bhatt DL, Bittner VA, Diaz R, Edelberg JM, Goodman SG, Hanotin C, Harrington RA, Jukema JW, Lecorps G, Mahaffey KW, Moryusef A, Pordy R, Quintero K, Roe MT, Sasiela WJ, Tamby JF, Tricoci P, White HD and Zeiher AM: Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome. *The New England journal of medicine*, 2018; 379: 2097-2107
 - 22) Cho KH, Kim MC, Choo EH, Choi IJ, Lee SN, Park MW, Park CS, Kim HY, Kim CJ, Sim DS, Kim JH, Hong YJ, Jeong MH, Chang K and Ahn Y: Impact of Low Baseline Low-Density Lipoprotein Cholesterol on Long-Term Postdischarge Cardiovascular Outcomes in Patients With Acute Myocardial Infarction. *J Am Heart Assoc*, 2022; 11: e025958
 - 23) Jang AY, Lim S, Jo SH, Han SH and Koh KK: New Trends in Dyslipidemia Treatment. *Circ J*, 2021; 85: 759-768
 - 24) Patel KV, Pandey A and de Lemos JA: Conceptual Framework for Addressing Residual Atherosclerotic Cardiovascular Disease Risk in the Era of Precision Medicine. *Circulation*, 2018; 137: 2551-2553
 - 25) Yusuf S, Joseph P, Rangarajan S, Islam S, Mente A, Hystad P, Brauer M, Kutty VR, Gupta R, Wielgosz A, AlHabib KF, Dans A, Lopez-Jaramillo P, Avezum A, Lanas F, Oguz A, Kruger IM, Diaz R, Yusuf K, Mony P, Chifamba J, Yeates K, Kelishadi R, Yusufali A, Khatib R, Rahman O, Zatonska K, Iqbal R, Wei L, Bo H, Rosengren A, Kaur M, Mohan V, Lear SA, Teo KK, Leong D, O'Donnell M, McKee M and Dagenais G: Modifiable risk factors, cardiovascular disease, and mortality in 155 722 individuals from 21 high-income, middle-income, and low-income countries (PURE): a prospective cohort study. *Lancet (London, England)*, 2020; 395: 795-808
 - 26) Everett BM: Residual Inflammatory Risk: A Common and Important Risk Factor for Recurrent Cardiovascular Events. *J Am Coll Cardiol*, 2019; 73: 2410-2412
 - 27) Ridker PM: Inhibiting Interleukin-6 to Reduce Cardiovascular Event Rates: A Next Step for Atherothrombosis Treatment and Prevention. *J Am Coll Cardiol*, 2021; 77: 1856-1858
 - 28) Sato R, Akiyama E, Konishi M, Matsuzawa Y, Suzuki H, Kawashima C, Kimura Y, Okada K, Maejima N, Iwahashi N, Hibi K, Kosuge M, Ebina T, von Haehling S, Anker SD, Tamura K and Kimura K: Decreased Appendicular Skeletal Muscle Mass is Associated with Poor Outcomes after ST-Segment Elevation Myocardial Infarction. *J Atheroscler Thromb*, 2020; 27: 1278-1287
 - 29) Matsushita K, Hibi K, Komura N, Akiyama E, Maejima N, Iwahashi N, Tsukahara K, Kosuge M, Ebina T, Sumita S, Umemura S and Kimura K: Effects of 4 Statins on Regression of Coronary Plaque in Acute Coronary Syndrome. *Circ J*, 2016; 80: 1634-1643
 - 30) Furman D, Campisi J, Verdin E, Carrera-Bastos P, Targ S, Franceschi C, Ferrucci L, Gilroy DW, Fasano A, Miller GW, Miller AH, Mantovani A, Weyand CM, Barzilai N, Goronzy JJ, Rando TA, Effros RB, Lucia A, Kleinstreuer N and Slavich GM: Chronic inflammation in the etiology of disease across the life span. *Nature medicine*, 2019; 25: 1822-1832
 - 31) Sato R, Vatic M, da Fonseca GWP and von Haehling S: Sarcopenia and Frailty in Heart Failure: Is There a Biomarker Signature? *Current heart failure reports*, 2022; 19: 400-411
 - 32) Amarasekera AT, Chang D, Schwarz P and Tan TC: Does vascular endothelial dysfunction play a role in physical frailty and sarcopenia? A systematic review. *Age Ageing*, 2021; 50: 725-732
 - 33) Pandey A, Kitzman D and Reeves G: Frailty Is

- Intertwined With Heart Failure: Mechanisms, Prevalence, Prognosis, Assessment, and Management. *JACC Heart Fail*, 2019; 7: 1001-1011
- 34) Widlansky ME, Gokce N, Keaney JF, Jr. and Vita JA: The clinical implications of endothelial dysfunction. *J Am Coll Cardiol*, 2003; 42: 1149-1160
- 35) Godo S and Shimokawa H: Endothelial Functions. Arteriosclerosis, thrombosis, and vascular biology, 2017; 37: e108-e114
- 36) Alonso-Bouzon C, Carcaillon L, García-García FJ, Amor-Andrés MS, El Assar M and Rodríguez-Mañas L: Association between endothelial dysfunction and frailty: the Toledo Study for Healthy Aging. *Age (Dordr)*, 2014; 36: 495-505
- 37) Linden E, Cai W, He JC, Xue C, Li Z, Winston J, Vlassara H and Uribarri J: Endothelial dysfunction in patients with chronic kidney disease results from advanced glycation end products (AGE)-mediated inhibition of endothelial nitric oxide synthase through RAGE activation. *Clinical journal of the American Society of Nephrology: CJASN*, 2008; 3: 691-698
- 38) Ridker PM, MacFadyen JG, Everett BM, Libby P, Thuren T and Glynn RJ: Relationship of C-reactive protein reduction to cardiovascular event reduction following treatment with canakinumab: a secondary analysis from the CANTOS randomised controlled trial. *Lancet (London, England)*, 2018; 391: 319-328
- 39) Tardif JC, Kouz S, Waters DD, Bertrand OF, Diaz R, Maggioni AP, Pinto FJ, Ibrahim R, Gamra H, Kiwan GS, Berry C, López-Sendón J, Ostadal P, Koenig W, Angoulvant D, Grégoire JC, Lavoie MA, Dubé MP, Rhoads D, Provencher M, Blondeau L, Orfanos A, L'Allier PL, Guertin MC and Rouville F: Efficacy and Safety of Low-Dose Colchicine after Myocardial Infarction. *The New England journal of medicine*, 2019; 381: 2497-2505
- 40) Ridker PM, Everett BM, Pradhan A, MacFadyen JG, Solomon DH, Zaharris E, Mam V, Hasan A, Rosenberg Y, Iturriaga E, Gupta M, Tsigoulis M, Verma S, Clearfield M, Libby P, Goldhaber SZ, Seagle R, Ofori C, Saklayen M, Butman S, Singh N, Le May M, Bertrand O, Johnston J, Paynter NP and Glynn RJ: Low-Dose Methotrexate for the Prevention of Atherosclerotic Events. *The New England journal of medicine*, 2019; 380: 752-762
- 41) Tong DC, Quinn S, Nasis A, Hiew C, Roberts-Thomson P, Adams H, Sriamaweswaran R, Htun NM, Wilson W, Stub D, van Gaal W, Howes L, Collins N, Yong A, Bhindi R, Whitbourn R, Lee A, Hengel C, Asrress K, Freeman M, Amerena J, Wilson A and Layland J: Colchicine in Patients With Acute Coronary Syndrome: The Australian COPS Randomized Clinical Trial. *Circulation*, 2020; 142: 1890-1900
- 42) Thomas RJ, Beatty AL, Beckie TM, Brewer LC, Brown TM, Forman DE, Franklin BA, Keteyian SJ, Kitzman DW, Regensteiner JG, Sanderson BK and Whooley MA: Home-Based Cardiac Rehabilitation: A Scientific Statement From the American Association of Cardiovascular and Pulmonary Rehabilitation, the American Heart Association, and the American College of Cardiology. *J Am Coll Cardiol*, 2019; 74: 133-153
- 43) Petersen AM and Pedersen BK: The anti-inflammatory effect of exercise. *Journal of applied physiology (Bethesda, Md: 1985)*, 2005; 98: 1154-1162
- 44) Bray NW, Smart RR, Jakobi JM and Jones GR: Exercise prescription to reverse frailty. *Applied physiology, nutrition, and metabolism=Physiologie appliquee, nutrition et metabolisme*, 2016; 41: 1112-1116
- 45) Virani SS, Brautbar A, Davis BC, Nambi V, Hoogeveen RC, Sharrett AR, Coresh J, Mosley TH, Morrisett JD, Catellier DJ, Folsom AR, Boerwinkle E and Ballantyne CM: Associations between lipoprotein(a) levels and cardiovascular outcomes in black and white subjects: the Atherosclerosis Risk in Communities (ARIC) Study. *Circulation*, 2012; 125: 241-249
- 46) LaRosa JC, Grundy SM, Waters DD, Shear C, Barter P, Fruchart JC, Gotto AM, Greten H, Kastelein JJ, Shepherd J and Wenger NK: Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *The New England journal of medicine*, 2005; 352: 1425-1435
- 47) Fyfe T, Baxter RH, Cochran KM and Booth EM: Plasma-lipid changes after myocardial infarction. *Lancet (London, England)*, 1971; 2: 997-1001
- 48) Rosenson RS: Myocardial injury: the acute phase response and lipoprotein metabolism. *J Am Coll Cardiol*, 1993; 22: 933-940



Supplemental Fig. 1. Receiver-operating characteristic curve defining the optimal LDL-C cut-off value for composite primary outcome prediction

LDL-C, low-density lipoprotein cholesterol; AUC, area under the curve



Supplemental Fig. 2. Kaplan-Meier curves of cumulative event-free rate for primary and secondary composite outcomes in patients taking strong statins in the low and high LDL-C groups

(A) Primary composite outcome (B) Secondary composite outcome
 LDL-C, low-density lipoprotein cholesterol.

Supplemental Table 1. Factors associated with the primary composite outcome

Variables	Univariate analysis		
	HR	95% CI	<i>p</i> -value
Age, years	1.06	1.04-1.09	<0.0001
Male	0.80	0.46-1.39	0.43
Body mass index, per 1 kg/m ²	0.94	0.88-1.01	0.08
Hypertension	0.97	0.61-1.54	0.90
Diabetes mellitus	1.71	1.08-2.71	0.02
Current smoker	0.89	0.57-1.41	0.63
History of MI	1.85	0.80-4.28	0.15
With cancer	0.60	0.15-2.44	0.47
eGFR on admission, per 10 mL/min/1.73m ²	0.84	0.75-0.94	0.003
HDL-C on admission, per 10 mg/dL	0.92	0.76-1.09	0.36
LDL-C on admission, per 10 mg/dL	0.99	0.98-0.99	0.0007
LDL-C after discharge (1 month), per 10 mg/dL (<i>n</i> = 335)	0.90	0.80-1.01	0.08
Reduction in LDL-C levels after discharge (1 month), per 10 mg/dL (<i>n</i> = 335)	0.93	0.86-1.00	0.05
TG on admission, per 10 mg/dL	0.97	0.94-0.99	0.02
BNP on admission, per 100 pg/mL	1.13	1.07-1.19	<0.0001
hs-CRP ≥ 0.2 mg/dL on admission	1.02	0.65-1.61	0.92
hs-CRP ≥ 0.2 mg/dL in the chronic phase (<i>n</i> = 399)	1.85	1.13-3.02	0.01
GNRI < 92	2.37	1.28-4.42	0.006
LVEF on admission, per 10%	0.70	0.57-0.85	0.0003
STEMI	1.42	0.82-2.47	0.22
Multivessel disease	1.59	1.01-2.51	0.04
Medication at discharge			
Beta blocker	1.37	0.84-2.21	0.21
ACE-I or ARB	1.16	0.64-2.11	0.63
Strong statin	0.50	0.26-0.99	0.04
Gait speed, per 0.1 m/s (344 patients)	0.82	0.74-0.92	0.0006
Ln RHI, per 0.1	0.78	0.71-0.86	<0.0001
Low LDL-C group	2.66	1.66-4.26	<0.0001

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BNP, B- type natriuretic peptide; eGFR, estimated glomerular filtration rate; GNRI, geriatric nutritional risk index; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; Ln RHI, logarithmic value of reactive hyperemia index; LVEF, left ventricular ejection fraction; MI, myocardial infarction; STEMI, ST-segment elevation myocardial infarction; TG, triglycerides.

Supplemental Table 2. Baseline characteristics of patients with and without primary outcome in the low LDL-C group

	Primary outcome			<i>p</i> -value
	Overall (<i>n</i> = 172)	Present (<i>n</i> = 49)	Absent (<i>n</i> = 123)	
Age, years	68 ± 12	74 ± 11	66 ± 12	< 0.0001
Male sex, <i>n</i> (%)	147 (85.5)	39 (79.6)	108 (87.8)	0.17
Body mass index, kg/m ²	23.9 ± 3.7	23.5 ± 3.6	24.1 ± 3.8	0.24
Hypertension, <i>n</i> (%)	111 (65.3)	29 (59.2)	83 (67.5)	0.30
Diabetes mellitus, <i>n</i> (%)	65 (38.2)	20 (40.8)	46 (37.4)	0.68
Current smoker, <i>n</i> (%)	81 (47.9)	23 (47.9)	59 (48.0)	0.99
History of MI, <i>n</i> (%)	6 (3.5)	3 (6.1)	3 (2.4)	0.23
With cancer, <i>n</i> (%)	8 (4.7)	2 (4.1)	6 (4.9)	0.82
eGFR on admission, mg/dL	66.3 [51.6-75.1]	59.7 [48.3-73.7]	66.8 [55.4-77.6]	0.17
HDL-C on admission, mg/dL	42 [37-51]	43 [37-54]	41 [36-51]	0.79
LDL-C on admission, mg/dL	103 [92-113]	105 [93-112]	101 [92-114]	0.85
LDL-C after discharge (1 month), mg/dL	70 [57-83]	71 [60-82]	69 [57-85]	0.99
TG on admission, mg/dL	119 [76-192]	103 [73-158]	124 [80-226]	0.07
BNP on admission, pg/mL	57 [25-151]	82 [44-250]	43 [22-121]	0.004
hs-CRP ≥ 0.2 mg/dL on admission, <i>n</i> (%)	79 (45.9)	21 (42.9)	58 (47.2)	0.61
hs-CRP ≥ 0.2 mg/d in the chronic phase, <i>n</i> (%)	43 (25.4)	18 (36.7)	25 (20.8)	0.03
GNRI < 92, <i>n</i> (%)	17 (9.9)	6 (12.2)	11 (9.0)	0.52
LVEF on admission, %	50 ± 12	47 ± 13	51 ± 12	0.14
STEMI, <i>n</i> (%)	117 (68.0)	38 (77.6)	79 (64.2)	0.09
Multivessel disease, <i>n</i> (%)	82 (47.7)	31 (63.3)	51 (41.5)	0.01
Medication at discharge				
Aspirin, <i>n</i> (%)	170 (98.8)	49 (100)	121 (98.4)	0.37
Beta blockers, <i>n</i> (%)	102 (59.7)	31 (63.3)	71 (58.2)	0.54
ACE-I or ARB, <i>n</i> (%)	137 (79.7)	39 (79.6)	98 (79.7)	0.99
Strong statin, <i>n</i> (%)	146 (84.9)	39 (79.6)	107 (87.0)	0.22
Gait speed, m/s	0.84 ± 0.22	0.74 ± 0.21	0.88 ± 0.21	0.0007
Ln RHI	0.57 ± 0.26	0.47 ± 0.28	0.60 ± 0.24	0.005

Variables are expressed as numbers (percentages), mean ± SD, or median [25th-75th percentile]. ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BNP, B- type natriuretic peptide; eGFR, estimated glomerular filtration rate; GNRI, geriatric nutritional risk index; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; Ln RHI, logarithmic value of reactive hyperemia index; LVEF, left ventricular ejection fraction; MI, myocardial infarction; SD, standard deviation; STEMI, ST-segment elevation myocardial infarction; TG, triglycerides.

Supplemental Table 3. Factors associated with the primary composite outcome in the low LDL-C group

Variables	Univariate analysis		
	HR	95% CI	<i>p</i> -value
Age, years	1.06	1.03-1.09	0.0001
Male	0.60	0.30-1.20	0.15
Body mass index, per 1 kg/m ²	0.96	0.88-1.04	0.30
Hypertension	0.71	0.40-1.26	0.25
Diabetes mellitus	1.09	0.61-1.93	0.77
Current smoker	0.98	0.55-1.72	0.93
History of MI	2.10	0.65-6.79	0.21
With cancer	0.93	0.23-3.84	0.92
eGFR on admission, per 10 mL/min/1.73m ²	0.90	0.77-1.05	0.20
HDL-C on admission, per 10 mg/dL	0.97	0.78-1.17	0.77
LDL-C on admission, per 10 mg/dL	0.99	0.98-1.02	0.96
LDL-C after discharge (1 month), per 10 mg/dL	0.95	0.80-1.11	0.52
Reduction in LDL-C levels after discharge (1 month), per 10 mg/dL	1.06	0.93-1.21	0.40
TG on admission, per 10 mg/dL	0.98	0.95-1.00	0.11
BNP on admission, per 100 pg/mL	1.09	0.96-1.21	0.12
hs-CRP ≥ 0.2 mg/dL on admission	1.01	0.57-1.78	0.98
hs-CRP ≥ 0.2 mg/dL in the chronic phase	1.92	1.07-3.46	0.03
GNRI < 92	1.14	0.48-2.69	0.77
LVEF on admission, per 10%	0.82	0.66-1.03	0.09
STEMI	1.73	0.88-3.40	0.11
Multivessel disease	1.79	0.99-3.21	0.05
Medication at discharge			
Beta blocker	1.17	0.66-2.10	0.59
ACE-I or ARB	1.02	0.50-2.04	0.96
Strong statin	0.73	0.36-1.46	0.37
Gait speed, per 0.1 m/s	0.81	0.71-0.93	0.002
Ln RHI, per 0.1	0.83	0.73-0.94	0.003

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BNP, B- type natriuretic peptide; eGFR, estimated glomerular filtration rate; GNRI, geriatric nutritional risk index; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; Ln RHI, logarithmic value of reactive hyperemia index; LVEF, left ventricular ejection fraction; MI, myocardial infarction; STEMI, ST-segment elevation myocardial infarction; TG, triglycerides.

Supplemental Table 4. Factors associated with the primary composite outcome in the high LDL-C group

Variables	Univariate analysis		
	HR	95% CI	<i>p</i> -value
Age, years	1.05	1.02-1.09	0.003
Male	0.88	0.36-2.19	0.79
Body mass index, per 1 kg/m ²	0.91	0.81-1.03	0.15
Hypertension	1.25	0.57-2.74	0.57
Diabetes mellitus	2.59	1.19-5.60	0.02
Current smoker	0.81	0.38-1.73	0.59
History of MI	2.31	0.69-7.75	0.17
With cancer	1.92	-	0.99
eGFR on admission, per 10 mL/min/1.73m ²	0.81	0.67-0.98	0.03
HDL-C on admission, per 10 mg/dL	0.90	0.64-1.25	0.56
LDL-C on admission, per 10 mg/dL	0.99	0.98-1.01	0.68
LDL-C after discharge (1 month), per 10 mg/dL	0.96	0.78-1.15	0.64
Reduction in LDL-C levels after discharge (1 month), per 10 mg/dL	0.99	0.85-1.13	0.88
TG on admission, per 10 mg/dL	0.93	0.86-0.98	0.02
BNP on admission, per 100 pg/mL	1.17	1.08-1.25	<0.0001
hs-CRP ≥ 0.2 mg/dL on admission	1.17	0.55-2.51	0.68
hs-CRP ≥ 0.2 mg/dL in the chronic phase	1.37	0.55-3.44	0.50
GNRI < 92	6.27	2.48-15.88	0.0001
LVEF on admission, per 10%	0.51	0.35-0.73	0.0002
STEMI	1.34	0.51-3.53	0.56
Multivessel disease	1.13	0.53-2.41	0.76
Medication at discharge			
Beta blocker	2.06	0.83-5.11	0.12
ACE-I or ARB	1.83	0.55-6.08	0.33
Strong statin	-	-	0.99
Gait speed, per 0.1 m/s	0.89	0.74-1.09	0.25
Ln RHI, per 0.1	0.72	0.61-0.84	<0.0001

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BNP, B- type natriuretic peptide; eGFR, estimated glomerular filtration rate; GNRI, geriatric nutritional risk index; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; Ln RHI, logarithmic value of reactive hyperemia index; LVEF, left ventricular ejection fraction; MI, myocardial infarction; STEMI, ST-segment elevation myocardial infarction; TG, triglycerides.