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ORIGINAL RESEARCH

Impact of Low Baseline Low-Density Lipoprotein Cholesterol on Long-Term Postdischarge Cardiovascular Outcomes in Patients With Acute Myocardial Infarction

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BACKGROUND: Real-world data on low baseline low-density lipoprotein cholesterol (LDL-C) levels and long-term postdischarge cardiovascular outcomes in patients with acute coronary syndrome are limited.

METHODS AND RESULTS: Of the 10 719 patients enrolled in the Korean registry of acute myocardial infarction between January 2004 and August 2014, we identified 5532 patients who were event free from death, recurrent myocardial infarction, or stroke during the in-hospital period after successful percutaneous coronary intervention. The co–primary outcomes were 3-point major adverse cardiovascular events (a composite of nonfatal stroke, nonfatal myocardial infarction, and cardiovascular death) and cardiovascular death at 5 years. Of 5532 patients with acute myocardial infarction (mean age, 62.1±12.8 years; 75.0% men), 446 cardiovascular deaths (8.1%) and 695 three-point major adverse cardiovascular events (12.6%) occurred at 5 years. In the continuous analysis of LDL-C, the risk of cardiovascular events increased steeply as LDL-C levels decreased from 100 mg/dL. For categorical analysis of LDL-C (<70, 70–99, and ≥100 mg/dL), as LDL-C levels decreased, clinical outcomes worsened (237/3759 [6.3%] in LDL-C ≥100 mg/dL versus 123/1291 [9.5%] in LDL-C 70–99 mg/dL versus 86/482 [17.8%] in LDL-C <70 mg/dL for cardiovascular death; *P*-trend<0.001; and 417/3759 [11.1%] in LDL-C ≥100 mg/dL versus 172/1291 [13.3%] in LDL-C 70–99 mg/dL versus 106/482 [22.2%] in LDL-C <70 mg/dL for 3-point major adverse cardiovascular event; *P*-trend<0.001). In a Cox time-to-event multivariable model with LDL-C levels ≥100 mg/dL as the reference, the baseline LDL-C level <70 mg/dL was independently associated with an increased incidence of cardiovascular death (adjusted hazard ratio, 1.68 [95% CI, 1.30–2.17]) and 3-point major adverse cardiovascular event (adjusted hazard ratio, 1.37 [95% CI, 1.10–1.71]).

CONCLUSIONS: In this Korean acute myocardial infarction registry, the baseline LDL-C level <70 mg/dL was significantly associated with an increased incidence of long-term cardiovascular events after discharge. (COREA [Cardiovascular Risk and Identification of Potential High-Risk Population]-Acute Myocardial Infarction Registry; NCT02806102).

REGISTRATION: URL: https://www.clinicaltrials.gov/; Unique identifier: NCT02806102.

Key Words: acute coronary syndrome ■ cholesterol, LDL ■ myocardial infarction ■ percutaneous coronary intervention

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CLINICAL PERSPECTIVE

What Is New?

- In the Korean registry of acute myocardial infarction with 5 years of follow-up, the risk of major cardiovascular events increased steeply as the baseline low-density lipoprotein cholesterol levels decreased from 100 mg/dL in event-free patients during the in-hospital period after successful percutaneous coronary intervention.
- A baseline low-density lipoprotein cholesterol level <70 mg/dL was associated with an increased incidence of major cardiovascular events after multivariable adjustments.

What Are the Clinical Implications?

- These results highlight the cholesterol paradox between very low baseline low-density lipoprotein cholesterol levels, which are considered to be markers of poor health status, and long-term postdischarge cardiovascular outcomes in patients with acute myocardial infarction.
- Meticulous attention is needed when assessing the future risk of long-term cardiovascular events and implementing an optimal lipid-lowering therapy in patients with acute myocardial infarction and low baseline low-density lipoprotein cholesterol levels, especially <70 mg/dL.

Nonstandard Abbreviations and Acronyms

3P-MACE	3-point major adverse cardiovascular event

The cumulative arterial burden of low-density lipoprotein cholesterol (LDL-C) drives the development and progression of atherosclerotic cardiovascular disease,[1] and LDL-C reduction therapy is beneficial in primary and secondary prevention of atherosclerotic cardiovascular disease.[2,3] There has been an increasing emphasis on achieving lower LDL-C levels by intensifying statins and administering ezetimibe or proprotein convertase subtilisin/kexin type 9 monoclonal antibodies.[4,5] However, a recent meta-analysis of 34 randomized clinical trials demonstrated that more intensive, compared with less intensive, LDL-C lowering was associated with a reduction in the risk of total and cardiovascular mortality in patients with baseline LDL-C levels ≥100 mg/dL, but not in those with baseline LDL-C levels <100 mg/dL.[6] This analysis supports individualizing the estimates of potential cardiovascular risk reduction derived from lipid-lowering therapy based on a patient's risk profile and magnitude of LDL-C reduction and the baseline LDL-C levels.[7]

Several studies demonstrated that lower baseline LDL-C levels are associated with an increased incidence of cardiovascular events during short- and mid-term follow-up after acute myocardial infarction (AMI).[8–10] Furthermore, a negative association has been reported between low baseline LDL-C levels and better clinical outcomes in patients with heart failure and stroke.[11,12] However, real-world data on low baseline LDL-C levels and long-term clinical outcomes in patients with acute coronary syndrome are limited. Hence, we aimed to investigate the long-term prognostic value of low baseline LDL-C levels after discharge in patients with AMI undergoing successful percutaneous coronary intervention (PCI) using a Korean registry.

METHODS

Study Population

The anonymized data that support the results of this study can be made available upon reasonable request. The COREA (Cardiovascular Risk and Identification of Potential High-Risk Population)-AMI registry was designed to evaluate the real-world features and long-term clinical outcomes in Korean patients with AMI between January 2004 and August 2014 (Data S1). The participating university hospitals used web-based registries to enroll all consecutive patients with AMI prospectively. Data about baseline characteristics, laboratory findings, and clinical outcomes were collected online by a clinical research coordinator. Mortality was verified by data collected from the National Health Insurance Service, which is single government-managed insurance that covers almost the entire Korean population. All study participants provided written informed consent obtained in a manner consistent with the Declaration of Helsinki. The study protocol was approved by the ethics committee of each participating center (institutional review board approval number: CNUH-2016-017). This study was registered at ClinicalTrials.gov (NCT02806102). Out of 10 719 patients enrolled in the COREA-AMI, we identified 8624 consecutive patients with AMI not receiving lipid-lowering therapy at the time of admission and underwent successful PCI (Figure 1). Patients who died or with recurrent myocardial infarction or stroke during the in-hospital period or without persistence with statin therapy for up to 3 years were excluded. Consequently, 5532 patients with AMI (age, 62.1±12.8 years; 75.0% men) were analyzed.

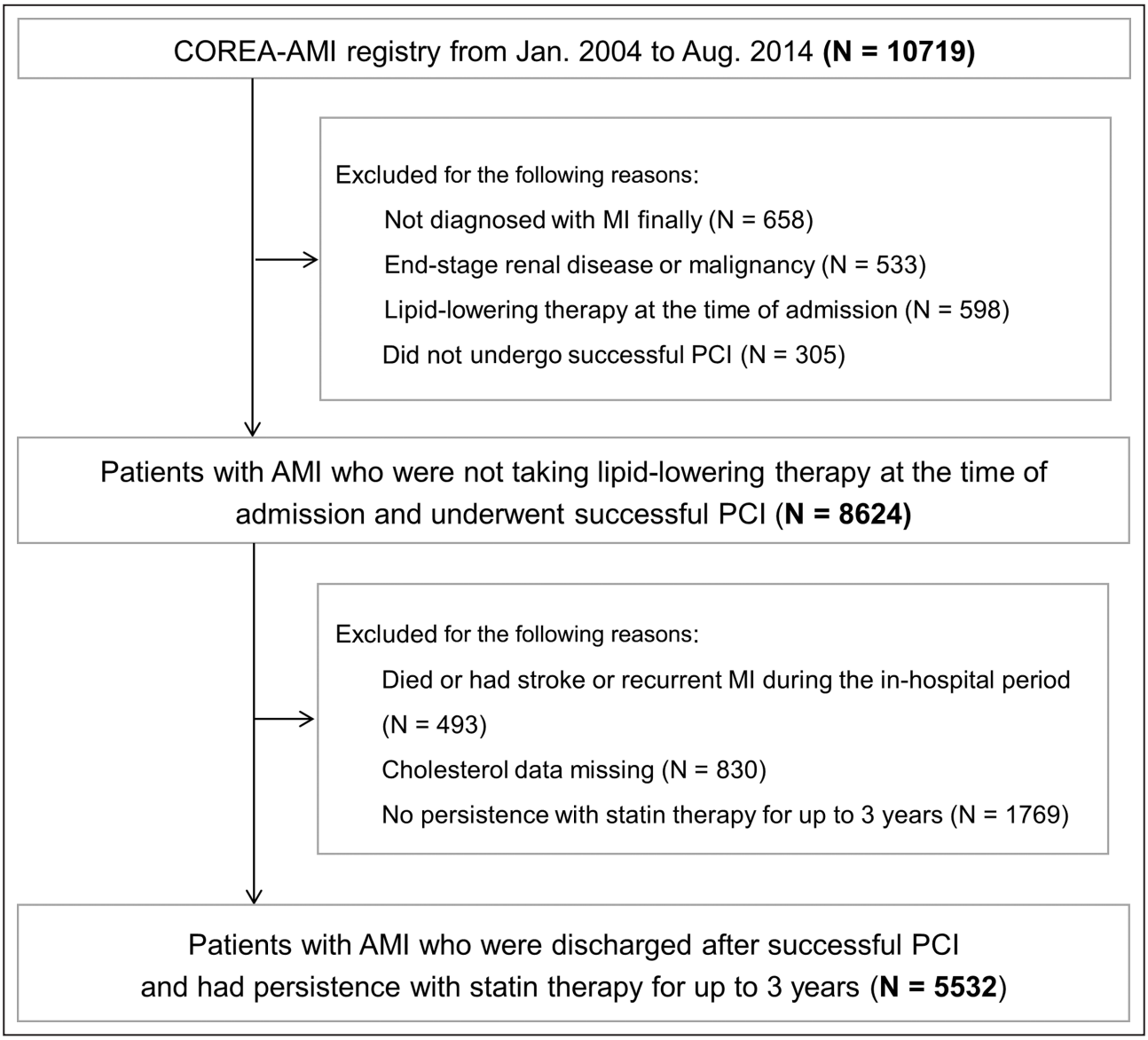

Figure 1. Description of the study population.
Of 10719 patients enrolled in the COREA (Cardiovascular Risk and Identification of potential high-risk population)–AMI (Acute Myocardial Infarction) registry, 658 were excluded because they were not diagnosed with MI finally; 533 were excluded because of end-stage renal disease or malignancy. We identified 8624 patients with AMI who were not taking lipid-lowering therapy at the time of admission and underwent successful PCI. Of them, 493 were excluded because of death or recurrent MI or stroke during the in-hospital period; 830 were excluded because of missing cholesterol data; 1769 were excluded because of not having persistence with statin therapy for up to 3 years. MI indicates myocardial infarction; and PCI, percutaneous coronary intervention.

Percutaneous Coronary Intervention

Before PCI, all patients received loading doses of aspirin (300 mg) and a $P2Y_{12}$ inhibitor (clopidogrel 300–600 mg; ticagrelor 180 mg; or prasugrel 60 mg). PCI was performed according to the standard guidelines. The revascularization strategy, the route of catheterization, adjunctive drugs, and the use of intravascular imaging were selected according to the physician's discretion. After PCI, the patients were administered a lifelong dose of aspirin and a $P2Y_{12}$ inhibitor for >1 year, unless there was an inevitable reason for discontinuation. Optimal medical therapies, including statins, beta-blockers, and renin-angiotensin-aldosterone system blockers, were recommended according to the guidelines.

Outcomes and Definitions

The co–primary outcomes were first-ever 3-point major adverse cardiovascular events (3P-MACE; a composite of nonfatal stroke, nonfatal myocardial infarction, and cardiovascular death) and cardiovascular death for a period of up to 5 years. The secondary outcomes were nonfatal stroke, nonfatal myocardial infarction,

and cardiovascular death. AMI was diagnosed when there was an elevated cardiac enzyme level (>99th percentile upper reference limit) with evidence of myocardial ischemia, such as ischemic symptoms, ischemic electrocardiographic changes, or imaging evidence of myocardial ischemia. ST-segment–elevation myocardial infarction was diagnosed on the basis of a new ST-segment–elevation ≥0.1 mV in ≥2 contiguous leads (≥0.2 mV in V2–3 leads) or a new left bundle branch block with an increase in cardiac enzyme levels. Successful PCI was defined as residual stenosis of <30% with final Thrombolysis in Myocardial Infarction grade II or III flow. Persistence with statin therapy was defined as receiving a statin prescription at every 6-month follow-up. An overnight fasting blood sample was drawn for lipid measurements within 24 hours of admission. Lipid profiles were directly measured using routine analyses at local hospitals.

Statistical Analysis

Continuous variables are expressed as mean±SD or median (interquartile range) and were compared using 1-way analysis of variance or the Kruskal–Wallis test, as appropriate. Categorical variables are presented as the number of cases and percentages and were compared using the chi-square test or Fisher's exact test. For continuous analysis of LDL-C, a restricted cubic spline curve was used with reference LDL-C of 100 mg/dL. For categorical analysis of LDL-C, patients were classified into 3 groups according to the baseline LDL-C levels of <70, 70 to 99, and ≥100 mg/dL. Kaplan–Meier analysis of the primary end point according to the groups was performed using the log-rank test. A multivariable Cox regression analysis was performed to assess the correlates of clinical outcomes. We included the baseline variables with $P < 0.1$ in the univariable analysis and any other baseline variables judged to be of clinical relevance from previously published literature after considering the assumption of proportionality and linearity of the Cox proportional hazards model. Specifically, these variables comprised age, sex, body mass index, diagnosis of ST-segment–elevation myocardial infarction, Killip class, heart rate, systolic blood pressure, anemia, creatinine clearance, left ventricular ejection fraction, LDL-C levels, high-sensitivity C-reactive protein, diabetes, hypertension, previous myocardial infarction or revascularization, family history of premature coronary artery disease, current smoker status, previous cerebrovascular accident, previous aortic disease or peripheral arterial occlusive disease, left anterior descending artery stenosis, multivessel coronary disease, preprocedural Thrombolysis in Myocardial Infarction flow grade 0, drug-eluting stent implantation, statin intensity at discharge, antiplatelet agents at discharge, beta-blocker at discharge, and renin-angiotensin-aldosterone system blockers at discharge. The linearity assumption was assessed using the cumulative sum of martingale-based residuals. The proportionality assumption was checked using log-minus-log plots. Collinearity diagnostics were assessed using the variance inflation factor and eigensystem analysis among variables included in the multivariable Cox regression analysis. The following variables with missing values were included in the multivariable analysis: creatinine clearance (n=1), systolic blood pressure (n=41), heart rate (n=42), body mass index (n=135), left ventricular ejection fraction (n=236), Killip class at presentation (n=502), and high-sensitivity C-reactive protein (n=740). Missing data were handled using the multiple imputation method. For sensitivity analyses, we examined clinical outcomes according to baseline LDL-C strata in diverse subpopulations by drug-eluting stents implantation, diagnosis of ST-segment–elevation myocardial infarction, and high-risk features. A 2-sided P value <0.05 was considered to indicate statistical significance, and analyses were performed using R software version 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria). This study was reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.

RESULTS

The mean baseline LDL-C level was 117.9±37.3 mg/dL. In the restricted cubic spline regression analysis, the risk of cardiovascular events increased steeply as the baseline LDL-C levels decreased from 100 mg/dL (Figure 2). The patients were classified into 3 LDL-C strata; 8.7% (482/5532) in LDL-C <70 mg/dL, 23.3% (1291/5532) in LDL-C 70 to 99 mg/dL, and 68.0% (3759/5532) in LDL-C ≥100 mg/dL.

Baseline Clinical and Angiographic Findings by Baseline LDL-C Strata

Compared with patients with LDL-C ≥100 mg/dL, those with LDL-C <70 mg/dL were older; more likely to have low body mass index, low systolic blood pressure, high heart rate, high Killip class at admission, low left ventricular ejection fraction, low hemoglobin levels, low creatinine clearance, and high high-sensitivity C-reactive protein levels. They were also more likely to have a history of hypertension, diabetes, myocardial infarction or revascularization, and cerebrovascular accident, and less likely to be current smokers (Table 1). Patients with LDL-C <70 mg/dL were more likely to have left main coronary stenosis and drug-eluting stent implantation and less likely to receive high-intensity statins (Table 2).

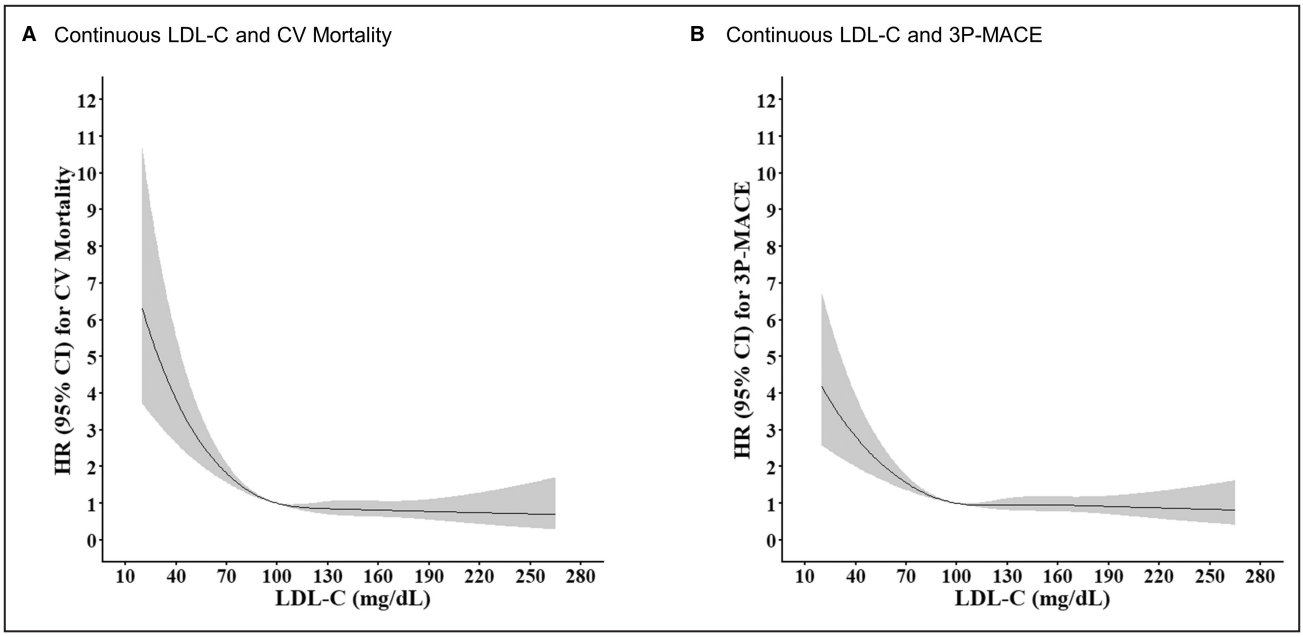

Figure 2. Continuous LDL-C levels and cardiovascular outcomes.
Continuous LDL-C levels and (**A**) cardiovascular mortality or (**B**) 3P-MACE. Solid lines and shared areas indicate hazard ratios and 95% CIs, respectively. 3P-MACE is defined as a composite of nonfatal stroke, nonfatal myocardial infarction, and cardiovascular death. 3P-MACE indicates 3-point major adverse cardiovascular event; CV, cardiovascular; HR, hazard ratio; and LDL-C, low-density lipoprotein cholesterol.

Clinical Outcomes According to the Baseline LDL-C Strata

The clinical outcomes were evaluated for up to 5 years (median, 1825 days; interquartile range, 1291–1825 days). Among the 5532 patients with AMI, there were 446 cardiovascular deaths, 198 myocardial infarctions, 173 cerebrovascular accidents, and 695 3P-MACEs at 5 years (Table S1). As the baseline LDL-C levels decreased, the clinical outcomes worsened (237 of 3759 patients with LDL-C ≥100 mg/dL [6.3%] versus 123 of 1291 patients with LDL-C 70–99 mg/dL [9.5%] versus 86 of 482 patients with LDL-C <70 mg/dL [17.8%] for cardiovascular death; *P*-trend <0.001; and 417 of 3759 patients with LDL-C ≥100 mg/dL [11.1%] versus 172 of 1291 patients with LDL-C 70–99 mg/dL [13.3%] versus 106 of 482 patients with LDL-C <70 mg/dL [22.2%] for 3P-MACE; *P*-trend <0.001). Kaplan–Meier curves for cardiovascular mortality and 3P-MACE by the baseline LDL-C strata over 5 years are shown in Figure 3. Clinical outcomes according to LDL-C strata in patients with LDL-C ≥100 mg/dL are presented in Table S2.

Prognostic Values of Low Baseline LDL-C Levels

The multivariable Cox regression analysis with LDL-C level ≥100 mg/dL as the reference revealed that the baseline LDL-C level <70 mg/dL was independently associated with an increased incidence of cardiovascular death (adjusted hazard ratio [HR], 1.68 [95% CI, 1.30–2.17]; *P*<0.001) and 3P-MACE (adjusted HR, 1.37 [95% CI, 1.10–1.71]; *P*=0.006) at 5 years (Figure 4). The results of the stepwise Cox proportional hazard models for correlates of cardiovascular death and 3P-MACE are presented in Tables S3 and S4, respectively.

Sensitivity Analysis

We performed a sensitivity analysis to ensure the robustness of the results. First, results from the Kaplan–Meier analysis and Cox time-to-event analysis in patients receiving drug-eluting stent implantation revealed associations similar to our main analysis (Figure S1 and Tables S5 and S6). Second, the Kaplan–Meier curves for cardiovascular death and 3P-MACE were assessed according to the LDL-C strata in patients with ST-segment–elevation myocardial infarction or non–ST-segment–elevation myocardial infarction, which were consistent with the main analysis (Figure S2**)**. Third, there were significant differences in clinical outcomes between patients with LDL-C <70 mg/dL and those with LDL-C ≥100 mg/dL over 5 years in each subpopulation, including the older adults patients (≥65 years) as well as patients with diabetes, renal insufficiency (estimated glomerular filtration rate <60 mL/min per 1.73 m^2), and low left ventricular systolic function (<50%) (Figures S3 and S4). Finally, the clinical outcomes according to

Table 1. Baseline Clinical and Laboratory Findings According to LDL-C Strata

	Overall (N=5532)	LDL-C ≥100 (N=3759)	LDL-C 70–99 (N=1291)	LDL-C <70 (N=482)	*P* value*
Demographics					
Age, y	62.1 (12.8)	60.9 (12.7)	63.7 (12.6)	67.1 (12.6)	<0.001
Male sex	4150 (75.0%)	2787 (74.1)	1009 (78.2)	354 (73.4)	0.011
Initial presentation					
STEMI	3092 (55.9%)	2131 (56.7)	682 (52.8)	279 (57.9)	0.036
Body mass index, kg/m^2	24.3 (3.3)	24.5 (3.2)	24.1 (3.3)	23.2 (3.5)	<0.001
Systolic blood pressure, mm Hg	129.5 (26.1)	130.7 (25.9)	127.3 (25.7)	125.7 (27.9)	<0.001
Heart rate, beats/min	77.9 (17.8)	77.7 (17.1)	77.7 (18.8)	80.1 (20.4)	0.037
Killip class on admission					
I	3932 (78.2%)	2765 (80.1)	866 (75.5)	301 (69.5)	<0.001
II	442 (8.8%)	304 (8.8)	93 (8.1)	45 (10.4)	0.358
III	282 (5.6%)	166 (4.8)	78 (6.8)	38 (8.8)	<0.001
IV	374 (7.4%)	215 (6.2)	110 (9.6)	49 (11.3)	<0.001
Left ventricular ejection fraction, %	54.0 (10.8)	54.3 (10.5)	53.9 (11.1)	51.9 (11.9)	<0.001
Medical history					
Hypertension	2694 (48.7%)	1705 (45.4)	689 (53.4)	300 (62.2)	<0.001
Diabetes	1508 (27.3%)	911 (24.2)	412 (31.9)	185 (38.4)	<0.001
Previous myocardial infarction or revascularization	375 (6.8%)	158 (4.2)	123 (9.5)	94 (19.5)	<0.001
Previous cerebrovascular accident	301 (5.4%)	177 (4.7)	80 (6.2)	44 (9.1)	<0.001
Previous aorta or peripheral arterial occlusive disease	17 (0.3%)	10 (0.3)	6 (0.5)	1 (0.2)	0.494
Current smoker	2441 (44.1%)	1762 (46.9)	513 (39.7)	166 (34.4)	<0.001
Family history of premature coronary artery disease	172 (3.1%)	127 (3.4)	36 (2.8)	9 (1.9)	0.149
Laboratory profiles					
Hemoglobin level, g/dL	13.9 (2.0)	14.1±1.9	13.7±2.0	12.8±2.3	<0.001
eGFR (CKD-EPI), mL/min per 1.73 m^2	66.4 (22.0)	68.1±21.4	64.3±22.6	59.6±23.1	<0.001
Total cholesterol, mg/dL	182.8 (42.8)	201.7±35.5	150.6±20.7	121.2±26.1	<0.001
Triglyceride, mg/dL	128.3 (98.2)	134.1±92.7	119.3±105.4	107.2±114.5	<0.001
HDL-C, mg/dL	41.3 (10.6)	41.7±10.1	40.3±10.7	40.1±13.2	<0.001
LDL-C, mg/dL	117.9 (37.3)	136.7±28.6	86.5±8.4	55.6±12.5	<0.001
High-sensitivity C-reactive protein, mg/dL	0.7 (0.2–2.9)	0.6 (0.2–2.5)	0.7 (0.2–3.6)	1.0 (0.2–4.7)	0.002

Values are presented as mean (SD), median (interquartile range), or number (%). CKD-EPI indicates Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; and STEMI, ST-segment–elevation myocardial infarction.

*P-values are derived from the chi-square test or Fisher's exact test for categorical variables, when appropriate, and from 1-way analysis of variance F-test or Kruskal–Wallis test for continuous variables for between-group comparisons.

baseline LDL-C strata in statin nonadherent patients after discharge (n=1796) were analyzed; similar associations were observed (Table S7).

DISCUSSION

Our study found that the risk of long-term cardiovascular events increased steeply as the baseline LDL-C levels decreased from 100 mg/dL in event-free patients from death, recurrent myocardial infarction, or stroke during the in-hospital period after successful PCI for AMI. Compared with patients with higher baseline LDL-C levels (≥100 mg/dL), those with lower baseline LDL-C levels (<70 mg/dL) were older, less likely to be obese, more likely to have comorbidities, and more likely to have bad hemodynamic parameters on admission. The baseline LDL-C level <70 mg/dL was independently associated with an increased incidence of cardiovascular death and 3P-MACE at 5 years. This negative association between low baseline LDL-C levels and long-term prognosis was consistent throughout diverse subpopulations, even including statin nonadherent patients after discharge. To our knowledge, this is the first large-scale, real-world cohort

Table 2. Angiographic Findings and Data Regarding Medications According to LDL-C Strata

	Overall (N=5532)	LDL-C ≥100 (N=3759)	LDL-C 70–99 (N=1291)	LDL-C <70 (N=482)	*P* value*
Angiographic findings					
Transradial approach	969 (17.5)	698 (18.6)	199 (15.4)	72 (14.9)	0.048
Stenotic lesions					
Left main artery	299 (5.4)	175 (4.7)	87 (6.7)	37 (7.7)	0.001
Left anterior descending artery	4025 (72.8)	2806 (74.6)	898 (69.6)	321 (66.6)	<0.001
Left circumflex artery	2522 (45.6)	1732 (46.1)	581 (45.0)	209 (43.4)	0.472
Right coronary artery	2951 (53.3)	1994 (53.0)	682 (52.8)	275 (57.1)	0.230
Multivessel disease	2984 (53.9)	2048 (54.5)	681 (52.7)	255 (52.9)	0.499
Preprocedural TIMI flow					
0	2447 (44.2)	1665 (44.3)	569 (44.1)	213 (44.2)	0.990
1	294 (5.3)	206 (5.5)	61 (4.7)	27 (5.6)	0.556
2	867 (15.7)	606 (16.1)	185 (14.3)	76 (15.8)	0.311
3	1649 (29.8)	1088 (28.9)	413 (32.0)	148 (30.7)	0.107
Drug-eluting stent implantation	4967 (89.8)	3404 (90.6)	1152 (89.2)	411 (85.3)	0.001
Intravascular ultrasound during PCI	1132 (20.5)	773 (20.6)	257 (19.9)	102 (21.2)	0.813
Optical coherence tomography during PCI	18 (0.3)	12 (0.3)	4 (0.3)	2 (0.4)	0.934
Postprocedural TIMI flow					
2	63 (1.1)	37 (1.0)	17 (1.3)	9 (1.9)	0.180
3	5469 (98.9)	3722 (99.0)	1274 (98.7)	473 (98.1)	0.180
Medications at discharge					
Statin intensity					
High	1303 (23.6)	935 (24.9)	263 (20.4)	105 (21.8)	0.003
Moderate	3905 (70.6)	2615 (69.6)	946 (73.3)	344 (71.4)	0.038
Low	324 (5.9)	209 (5.6)	82 (6.4)	33 (6.8)	0.362
Aspirin	5454 (98.6)	3713 (98.8)	1268 (98.2)	473 (98.1)	0.229
Clopidogrel	4736 (85.6)	3217 (85.6)	1115 (86.4)	404 (83.8)	0.394
Potent $P2Y_{12}$ inhibitor	777 (14.0)	532 (14.2)	171 (13.2)	74 (15.4)	0.496
Beta-blocker	4658 (84.2)	3177 (84.5)	1067 (82.6)	414 (85.9)	0.161
ACEi or ARB	4389 (79.3)	3015 (80.2)	998 (77.3)	376 (78.0)	0.064
Anticoagulant	125 (2.3)	76 (2.0)	34 (2.6)	15 (3.1)	0.186

Values are presented as number (%). ACEi indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; LDL-C, low-density lipoprotein cholesterol; PCI, percutaneous coronary intervention; and TIMI, Thrombolysis in Myocardial Infarction.

**P*-values are derived from the chi-square test or Fisher's exact test for categorical variables, when appropriate, for between-group comparisons.

study to investigate the association between low baseline LDL-C levels and long-term postdischarge cardiovascular outcomes in event-free patients during the in-hospital period after successful PCI for AMI.

There has been a debate about the role of baseline LDL-C levels in influencing clinical outcomes among patients with acute coronary syndrome treated with lipid-lowering therapy. A previous meta-analysis involving 17 000 patients demonstrated that the benefit of LDL-C reduction did not depend on baseline LDL-C levels, with a 22% relative reduction in the incidence of major cardiovascular events per 38.7 mg/dL (1.0 mmol/L) of LDL-C in patients with LDL-C <77 mg/dL.[2] A recent analysis of the Improved Reduction of Outcomes: Vytorin Efficacy International Trial reported that adding ezetimibe to statin consistently reduced the risk of cardiovascular events in patients following acute coronary syndrome irrespective of the baseline LDL-C of 50 to <70 mg/dL (HR, 0.92 [95% CI, 0.80–1.05]), 70 to <100 mg/dL (HR, 0.93 [95% CI, 0.87–1.01]), or 100–125 mg/dL (HR, 0.94 [95% CI, 0.86–1.03]; *P*-interaction=0.95).[13] However, in the Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 analysis, a progressive reduction in the benefit of intensive lipid-lowering therapy with atorvastatin 80 mg

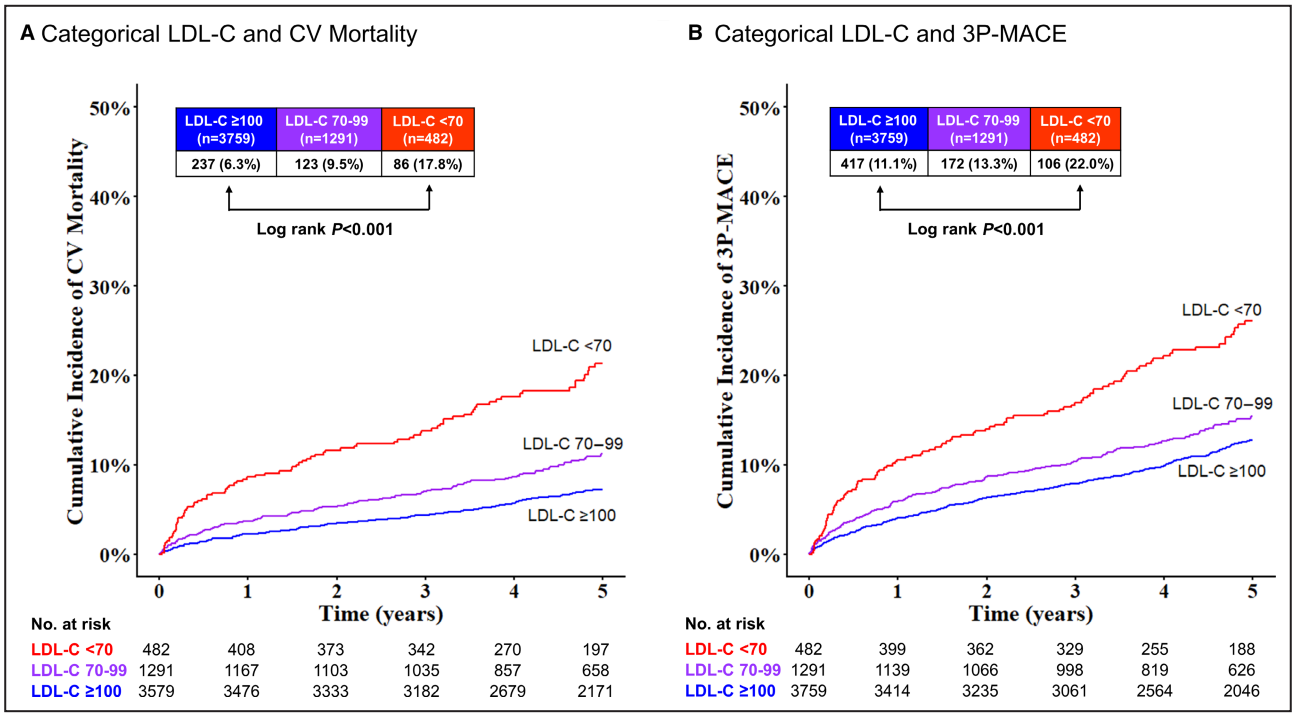

Figure 3. Categorical LDL-C levels and cardiovascular outcomes.
A, Cumulative incidence of CV mortality over 5 years according to LDL-C strata. **B**, Cumulative incidence of 3P-MACE over 5 years according to LDL-C strata. Kaplan–Meier analysis of the endpoint according to the groups was performed using a log-rank test. 3P-MACE indicates 3-point major adverse cardiovascular event; CV, cardiovascular; and LDL-C, low-density lipoprotein cholesterol.

over pravastatin 40 mg was observed in statin-naïve patients with acute coronary syndrome as baseline LDL-C levels declined; the hazards of the primary end points were 0.63 (95% CI, 0.47–0.85) in patients with baseline LDL-C >132 mg/dL and 0.93 (95% CI, 0.69–1.25) in those with baseline LDL-C <92 mg/dL (*P*-interaction=0.03).[14] A recent meta-analysis involving ≥130 000 patients across 34 trials investigated the association between the baseline LDL-C levels and total and cardiovascular mortality after LDL-C lowering[6]; more intensive compared with less intensive LDL-C reduction was associated with a greater reduction in the risk of total and cardiovascular mortality in trials of patients with higher baseline LDL-C levels; this association was not present when baseline LDL-C was <100 mg/dL. These findings may warrant the use of an integrated predictive model to quantify the net clinical benefit from lipid-lowering therapy, considering each patient's risk profile and baseline LDL-C levels.[7]

Several studies reported that lower baseline LDL-C levels are associated with an increased incidence of cardiovascular events after AMI, although conflicting results exist regarding the independent association between low baseline LDL-C levels and cardiovascular outcomes after AMI.[8–10] A nationwide Korean AMI cohort study involving 9571 patients between 2005 and 2008 demonstrated that patients with baseline LDL-C levels <70 mg/dL had remarkably high mortality rates at 12 months after PCI compared with those with LDL-C levels between 130 and 159 mg/dL, but the baseline LDL-C levels <70 mg/dL did not comprise an independent factor for increased mortality at 12 months.[8] A previous study based on a nationwide US AMI registry involving 115 492 patients reported that the risk of in-hospital mortality in the second to fourth quartiles of LDL-C levels was decreased (adjusted odds ratios, 0.79 [95% CI, 0.71–0.87], 0.80 [95% CI, 0.72–0.90]), and 0.85 (95% CI, [0.76–0.96], respectively) compared with the lowest quartile of LDL-C levels (<77 mg/dL).[10] LDL-C has been suggested to be one of the essential factors for cell survival after AMI whereby ischemia and reactive inflammation increases the vulnerability of the cell membrane.[15]

The cholesterol paradox has similarly been reported in patients with acute ischemic stroke, those with heart failure, and older adults.[11,12,16–18] A previous study involving 190 patients with acute ischemic stroke reported that low total cholesterol (<177.9 mg/dL) on admission was associated with older age and lower blood pressure, and it was an independent predictor of long-term mortality at 7 years.[12] Rauchhaus et al[11] analyzed 417 patients with chronic heart failure and demonstrated that lower serum total cholesterol levels were independently associated with a worse prognosis, after multivariable adjustments. They suggested a beneficial role of lipoproteins on immunologic

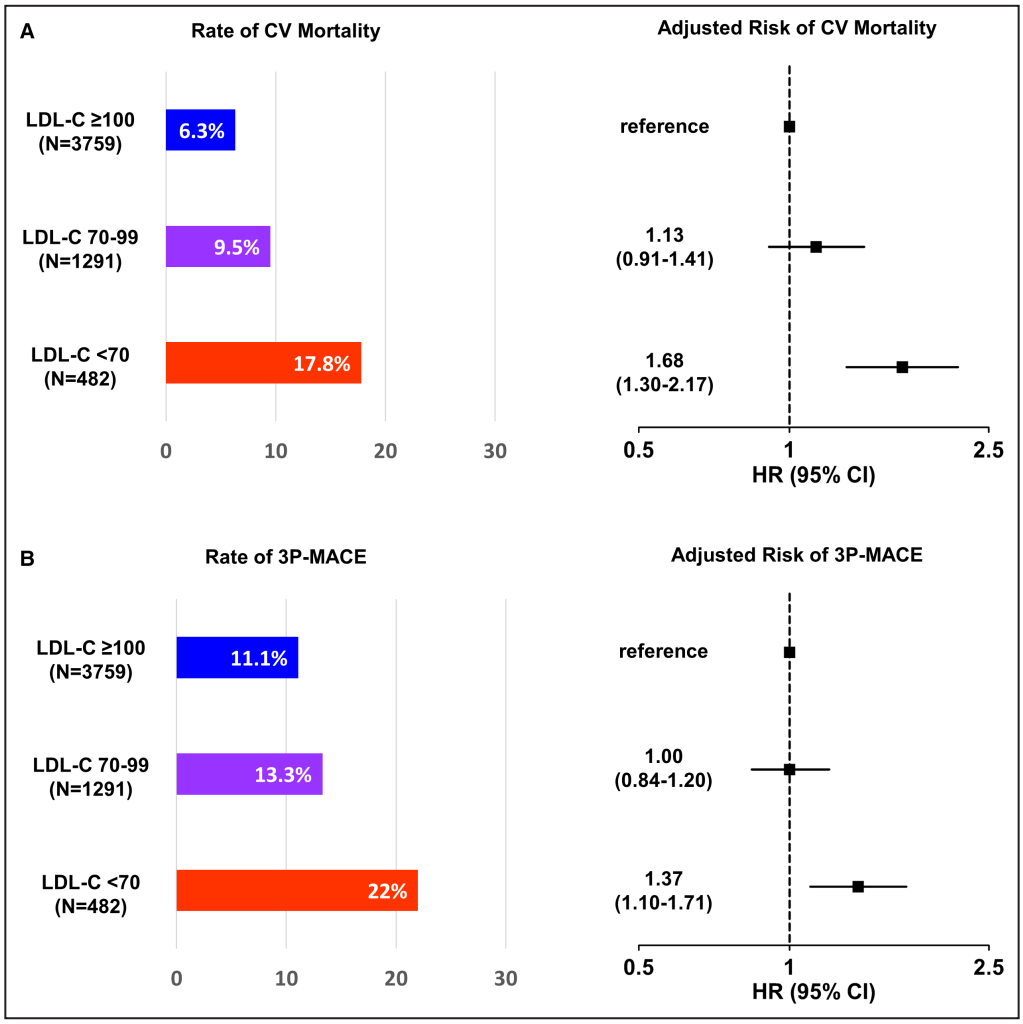

Figure 4. Adjusted risk of categorical LDL-C levels for cardiovascular outcomes.
Adjusted HRs for (**A**) CV mortality and (**B**) 3P-MACE at 5 years. Cox regression analysis using the backward elimination method was conducted. 3P-MACE indicates 3-point major adverse cardiovascular event; CV, cardiovascular; HR, hazard ratio; and LDL-C, low-density lipoprotein cholesterol.

modulation in patients with congestive heart failure. Additionally, low cholesterol levels might reflect an inadequate nutritional status or greater metabolic demands with a prognostic impact. During the 30-year follow-up period of the Framingham study, after 50 years of age, decreasing total cholesterol levels were associated with elevated overall mortality and cardiovascular mortality in males and females.[19] Iribarren et al[20] conducted a long-term prospective study involving 5941 middle-aged Japanese Americans, and suggested that a decline in serum total cholesterol levels occurs before the diagnosis of disease, including malignancy and chronic liver disease. A positive association between genetically predicted lifelong lowering of LDL-C and decreased frailty has been reported[21]; however, some cohort studies have suggested that low cholesterol levels were associated with a decline in functional performance or increased frailty.[22,23] Frailty is considered a systemic phenomenon in older adult patients with disrupted homeostasis, and an unexpected decline in the risk factor level (blood pressure or LDL-C levels) might indicate frailty. Frailty has been identified as an emerging risk factor for the development of cardiovascular events.[24]

Consistent evidence from numerous studies has established that reduction in the LDL-C levels by genetic mutations or lipid-lowering therapy is associated with a decreased incidence of atherosclerotic cardiovascular disease in a dose-dependent manner.[25–28] Furthermore, in a large clinical trial, lowering of LDL-C by proprotein convertase subtilisin/kexin type 9 inhibitors was found to be equally effective in reducing cardiovascular events in patients with atherosclerotic cardiovascular disease, regardless of whether the baseline LDL-C was <70 or ≥70 mg/dL.[29] In addition, lowering LDL-C levels to as low as <20 mg/dL did not

lead to safety concerns.[30] In the present study, patients with AMI who had lower baseline LDL-C levels were older and more likely to have low body mass index, low creatinine clearance, and more comorbidities than those with higher baseline LDL-C levels. These patients' characteristics are similar to those of patients in previous studies involving Taiwanese or American populations.[9,10] Taken together, the main finding of this study is that a negative association between low baseline LDL-C levels and long-term prognosis is likely attributable to poor health status, not the LDL-C per se or its treatment. Health care providers should strive to distinguish between low LDL-C levels attributable to genetic mutation or lipid-lowering therapy, and those attributable to poor health status when assessing the risk of long-term cardiovascular events.

Limitations

The findings of this study should be considered with the following limitations. First, the present study lacked detailed information about nutritional status or frailty, which might be associated with the risk of cardiovascular events long term. Second, LDL-C levels and other treatments during the follow-up period were not included in the analysis. However, we considered persistence with statin therapy for up to 3 years and performed multivariable adjustments using up to 24 risk factors. Third, blood samples for lipid measurement were collected at least several hours after admission to the index hospitals ("overnight fasting blood"). However, all the blood samples were collected within 24 hours of admission, and a previous study reported that mean lipid levels vary relatively little in the 4 days after the onset of the acute coronary syndrome.[31]

CONCLUSIONS

Based on a large, multicenter Korean AMI registry with 5 years of follow-up, we found that the risk of postdischarge cardiovascular events increased steeply as the baseline LDL-C levels decreased from 100 mg/dL after successful PCI. In the multivariable Cox regression analysis, a baseline LDL-C level <70 mg/dL was associated with an increased incidence of cardiovascular death and 3P-MACE after discharge. This negative association between low baseline LDL-C levels and long-term postdischarge cardiovascular outcomes was likely attributable to poor health status resulting in low baseline LDL-C levels. Meticulous attention is needed to assess the future risk of long-term cardiovascular events and implement an optimal lipid-lowering therapy in patients with AMI and low baseline LDL-C levels, especially <70 mg/dL. Further studies are warranted to clarify this issue.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Data S1
Tables S1–S7
Figures S1–S4

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SUPPLEMENTAL MATERIAL

Data S1. Supplemental Methods

COREA (CardiOvascular Risk and idEntificAtion of potential high-risk population)-AMI (Acute Myocardial Infarction) registry participating sites (number of patients) and investigators

1. Seoul St. Mary's Hospital, Seoul, Republic of Korea (1379 patients); Kiyuk Chang
2. Chonnam National University Hospital (3207), Gwangju, Republic of Korea; Youngkeun Ahn
3. Incheon St. Mary's Hospital (699), Incheon, Republic of Korea; Ik Jun Choi
4. St Vincent's Hospital (1194), Suwon, Republic of Korea; Su Nam Lee
5. Daejeon St. Mary's Hospital (1084), Daejeon, Republic of Korea; Mahn-Won Park
6. Yeouido St. Mary's Hospital (715), Seoul, Republic of Korea; Chul Soo Park
7. Bucheon St. Mary's Hospital (669), Bucheon, Republic of Korea; Hee-Yeol Kim
8. Uijeongbu St. Mary's Hospital (1772), Seoul, Republic of Korea; Chan Joon Kim

COREA-AMI registry inclusion and exclusion criteria

The inclusion criteria were (1) patients over 20 years of age, (2) those diagnosed with acute myocardial infarction based on the universal definition, and (3) those who underwent percutaneous coronary intervention. The exclusion criteria were (1) patients treated with conservative management and (2) those who refused to provide informed consent.

Table S1. Clinical outcomes according to baseline low-density lipoprotein cholesterol (LDL-C) strata.

	Overall (n = 5532)	**LDL-C ≥100 (n = 3759)**	**LDL-C 70–99 (n = 1291)**	**LDL-C <70 (n = 482)**	**P value***	**P-trend†**
Cardiovascular death	446 (8.1%)	237 (6.3%)	123 (9.5%)	86 (17.8%)	<0.001	<0.001
Non-fatal myocardial infarction	198 (3.6%)	137 (3.6%)	44 (3.4%)	17 (3.5%)	0.923	0.761
Non-fatal cerebrovascular accident	173 (3.1%)	126 (3.4%)	32 (2.5%)	15 (3.1%)	0.298	0.307
Three-point MACE	695 (12.6%)	417 (11.1%)	172 (13.3%)	106 (22.0%)	<0.001	<0.001

Values are presented as the number (%). *P values are derived from the chi-square test or Fisher's exact test, as appropriate, for between-group comparisons. †P values are calculated for linear trends across the groups. MACE, major adverse cardiocerebrovascular event.

Table S2. Clinical outcomes according to baseline low-density lipoprotein cholesterol (LDL-C) strata in patients with LDL-C ≥100 mg/dL.

	LDL-C ≥190 (n = 190)	**LDL-C 160-189 (n = 506)**	**LDL-C 130-159 (n = 1241)**	**LDL-C 100-129 (n = 1822)**	**P value***	**P-trend†**
Cardiovascular death	9 (4.7%)	34 (6.7%)	81 (6.5%)	113 (6.2%)	0.783	0.878
Non-fatal myocardial infarction	9 (4.7%)	19 (3.8%)	45 (3.6%)	64 (3.5%)	0.860	0.477
Non-fatal cerebrovascular accident	4 (2.1%)	12 (2.4%)	39 (3.1%)	71 (3.9%)	0.236	0.041
Three-point MACE	20 (10.5%)	52 (10.3%)	140 (11.3%)	205 (11.3%)	0.920	0.585

Values are presented as the number (%). *P values are derived from the chi-square test or Fisher's exact test, as appropriate, for between-group comparisons. †P values are calculated for linear trends across the groups. MACE, major adverse cardiocerebrovascular event.

Table S3. Results of Cox regression analysis applied to assess the correlates of cardiovascular mortality.

	Hazard Ratio (95% Confidence Interval)					
	No Adjustment	**P value**	**Model 1***	**P value**	**Model 2†**	**P value**
Age, years	1.09 (1.08-1.10)	<0.001	1.09 (1.08-1.10)	<0.001	1.08 (1.07-1.09)	<0.001
Left ventricular ejection fraction, %	0.95 (0.94-0.96)	<0.001			0.98 (0.97-0.99)	<0.001
LDL-C <70 mg/dL	3.23 (2.52-4.14)	<0.001	2.16 (1.68-2.78)	<0.001	1.68 (1.30-2.17)	<0.001
LDL-C 70−99 mg/dL	1.58 (1.27-1.96)	<0.001	1.30 (1.05-1.62)	0.018	1.13 (0.91-1.41)	0.275
Diabetes mellitus	2.14 (1.77-2.58)	<0.001			1.60 (1.32-1.94)	<0.001
Killip class >I	2.81 (2.33-3.39)	<0.001			1.46 (1.19-1.79)	<0.001
Anemia	3.24 (2.69-3.91)	<0.001			1.44 (1.17-1.76)	<0.001
High-sensitivity C-reactive protein >2mg/dL	2.07 (1.72-2.49)	<0.001			1.44 (1.18-1.74)	<0.001
eGFR (CKD-EPI) <60 mL/min/1.73 m^2	2.94 (2.42-3.57)	<0.001			1.43 (1.17-1.76)	<0.001
Current smoker	0.51 (0.42-0.63)	<0.001			1.40 (1.12-1.75)	0.003
Left anterior descending artery stenosis	1.52 (1.20-1.91)	<0.001			1.39 (1.09-1.77)	0.007
Previous cerebrovascular accident	2.64 (1.99-3.50)	<0.001			1.38 (1.03-1.84)	0.031
Heart rate >100 beats/minute	2.70 (2.13-3.42)	<0.001			1.34 (1.03-1.74)	0.027
Renin-angiotensin-aldosterone system blocker at discharge	0.64 (0.52-0.79)	<0.001			0.80 (0.64-0.99)	0.036
Drug-eluting stents implantation	0.55 (0.43-0.70)	<0.001			0.69 (0.53-0.89)	0.005
Male sex	0.45 (0.37-0.54)	<0.001	0.97 (0.79-1.19)	0.770	Eliminated	NA
Body mass index > 25 kg/m^2	0.53 (0.43-0.66)	<0.001			Eliminated	NA

STEMI diagnosis	0.70 (0.58-0.84)	<0.001			Eliminated	NA
Systolic blood pressure <100 mmHg	1.38 (1.01-1.87)	0.041			Eliminated	NA
Hypertension	1.99 (1.64-2.42)	<0.001			Eliminated	NA
Previous myocardial infarction or revascularization	2.05 (1.54-2.72)	<0.001			Eliminated	NA
Multivessel coronary disease	1.56 (1.29-1.90)	<0.001			Eliminated	NA
Preprocedural TIMI flow 0	0.76 (0.63-0.92)	0.005			Eliminated	NA
Potent $P2Y_{12}$ inhibitor at discharge	0.68 (0.49-0.94)	0.020			Eliminated	NA
High-intensity statin at discharge	1.10 (0.89-1.37)	0.380			Eliminated	NA

*Adjusted for age, sex, and LDL-C level. †Adjusted for age; sex; body mass index; STEMI diagnosis; Killip class; heart rate; systolic blood pressure; diabetes mellitus; hypertension; previous myocardial infarction or revascularization; anemia; creatinine clearance; left ventricular ejection fraction; LDL-C level; high sensitivity C-reactive protein; current smoker status; previous cerebrovascular accident; left anterior descending artery stenosis; multivessel coronary disease; preprocedural TIMI flow grade 0; drug-eluting stents implantation; high-intensity statin at discharge; potent $P2Y_{12}$ inhibitor at discharge; and renin-angiotensin-aldosterone system blockers at discharge. Cox regression analysis was performed using the backward elimination selection. CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; LDL-C, low-density lipoprotein cholesterol; NA, not applicable; STEMI, ST-segment elevation myocardial infarction; TIMI, Thrombolysis In Myocardial Infarction.

Table S4. Results of Cox regression analysis applied to assess the correlates of 3-point major adverse cardiovascular event (3P-MACE).

	Hazard Ratio (95% Confidence Interval)					
	No Adjustment	**P value**	**Model 1***	**P value**	**Model 2†**	**P value**
Age, years	1.06 (1.05-1.07)	<0.001	1.06 (1.05-1.07)	<0.001	1.05 (1.04-1.05)	<0.001
Left ventricular ejection fraction, %	0.97 (0.96-0.97)	<0.001			0.98 (0.98-0.99)	<0.001
LDL-C <70 mg/dL	2.26 (1.83-2.80)	<0.001	1.69 (1.36-2.10)	<0.001	1.37 (1.10-1.71)	0.006
LDL-C 70−99 mg/dL	1.25 (1.05-1.50)	0.012	1.09 (0.91-1.30)	0.349	1.00 (0.84-1.20)	0.970
Previous cerebrovascular accident	2.23 (1.75-2.85)	<0.001			1.44 (1.12-1.84)	0.004
Diabetes mellitus	1.81 (1.55-2.11)	<0.001			1.43 (1.22-1.67)	<0.001
Anemia	2.47 (2.12-2.87)	<0.001			1.40 (1.19-1.65)	<0.001
Killip class >I	2.07 (1.77-2.43)	<0.001			1.39 (1.18-1.64)	<0.001
High-sensitivity C-reactive protein >2mg/dL	1.77 (1.52-2.05)	<0.001			1.38 (1.18-1.61)	<0.001
eGFR (CKD-EPI) <60 mL/min/1.73 m^2	2.12 (1.83-2.47)	<0.001			1.34 (1.14-1.56)	<0.001
Left anterior descending artery stenosis	1.44 (1.20-1.73)	<0.001			1.32 (1.10-1.60)	0.004
Current smoker	0.62 (0.53-0.73)	<0.001			1.22 (1.02-1.45)	0.026
Body mass index > 25 kg/m^2	0.63 (0.53-0.74)	<0.001			0.85 (0.72-1.01)	0.060
Preprocedural TIMI flow 0	0.74 (0.63-0.86)	<0.001			0.80 (0.69-0.94)	0.006
Drug-eluting stents implantation	0.60 (0.49-0.74)	<0.001			0.66 (0.53-0.81)	<0.001
Male sex	0.57 (0.49-0.67)	<0.001	1.00 (0.85-1.19)	0.969	Eliminated	NA
STEMI diagnosis	0.76 (0.66-0.88)	<0.001			Eliminated	NA

Systolic blood pressure <100 mmHg	1.17 (0.90-1.51)	0.246			Eliminated	NA
Heart rate >100 beats/minute	1.73 (1.39-2.15)	<0.001			Eliminated	NA
Hypertension	1.58 (1.36-1.84)	<0.001			Eliminated	NA
Multivessel coronary disease	1.49 (1.28-1.74)	<0.001			Eliminated	NA
Potent $P2Y_{12}$ inhibitor at discharge	0.68 (0.52-0.88)	0.004			Eliminated	NA
High-intensity statin at discharge	1.06 (0.89-1.27)	0.490			Eliminated	NA
Renin-angiotensin-aldosterone system blocker at discharge	0.83 (0.70-1.00)	<0.001			Eliminated	NA
Beta-blocker at discharge	0.78 (0.65-0.95)	0.012			Eliminated	NA

*Adjusted for age, sex, and LDL-C level. †Adjusted for age; sex; body mass index; STEMI diagnosis; Killip class; heart rate; systolic blood pressure; diabetes mellitus; hypertension; anemia; creatinine clearance; left ventricular ejection fraction; LDL-C level; high sensitivity C-reactive protein; current smoker status; previous cerebrovascular accident; left anterior descending artery stenosis; multivessel coronary disease; preprocedural TIMI flow grade 0; drug-eluting stents implantation; high-intensity statin at discharge; potent $P2Y_{12}$ inhibitor at discharge; renin-angiotensin-aldosterone system blockers at discharge; and beta-blocker at discharge. Cox regression analysis was performed using the backward elimination selection. CKD-EPI, Chronic Kidney Disease Epidemiology. Collaboration; eGFR, estimated glomerular filtration rate; LDL-C, low-density lipoprotein cholesterol; NA, not applicable; STEMI, ST-segment elevation myocardial infarction; TIMI, Thrombolysis In Myocardial Infarction.

Table S5. Results of Cox regression analysis applied to assess the correlates of cardiovascular mortality in patients receiving drug-eluting stents implantation (n = 4967).

	Hazard Ratio (95% Confidence Interval)					
	No Adjustment	**P value**	**Model 1***	**P value**	**Model 2†**	**P value**
Age, years	1.09 (1.08-1.10)	<0.001	1.09 (1.07-1.10)	<0.001	1.07 (1.06-1.09)	<0.001
Left ventricular ejection fraction, %	0.95 (0.94-0.96)	<0.001			0.98 (0.97-0.99)	<0.001
LDL-C <70 mg/dL	3.27 (2.49-4.31)	<0.001	2.21 (1.67-2.92)	<0.001	1.69 (1.27-2.25)	<0.001
LDL-C 70−99 mg/dL	1.63 (1.28-2.07)	<0.001	1.35 (1.06-1.71)	0.015	1.17 (0.92-1.49)	0.193
Diabetes mellitus	2.30 (1.87-2.82)	<0.001			1.65 (1.34-2.04)	<0.001
High-sensitivity C-reactive protein >2mg/dL	2.20 (1.79-2.69)	<0.001			1.55 (1.26-1.91)	<0.001
Previous cerebrovascular accident	2.72 (2.01-3.68)	<0.001			1.50 (1.10-2.05)	0.011
Anemia	3.28 (2.67-4.02)	<0.001			1.49 (1.20-1.86)	<0.001
eGFR (CKD-EPI) <60 mL/min/1.73 m^2	2.90 (2.34-3.59)	<0.001			1.45 (1.16-1.82)	0.001
Heart rate >100 beats/minute	2.65 (2.05-3.44)	<0.001			1.42 (1.07-1.87)	0.015
Killip class >I	2.62 (2.13-3.23)	<0.001			1.42 (1.14-1.78)	0.002
Current smoker	0.53 (0.42-0.66)	<0.001			1.38 (1.08-1.76)	0.010
Left anterior descending artery stenosis	1.68 (1.29-2.20)	<0.001			1.37 (1.04-1.80)	0.026
Renin-angiotensin-aldosterone system blocker at discharge	0.60 (0.48-0.76)	<0.001			0.73 (0.58-0.91)	0.006
Body mass index > 25 kg/m^2	0.55 (0.44-0.70)	<0.001			Eliminated	NA

Preprocedural TIMI flow 0	0.74 (0.60-0.91)	0.005			Eliminated	NA
Male sex	0.50 (0.41-0.62)	<0.001	1.02 (0.82-1.27)	0.864	Eliminated	NA
STEMI diagnosis	0.71 (0.58-0.87)	0.001			Eliminated	NA
Systolic blood pressure <100 mmHg	1.31 (0.93-1.85)	0.125			Eliminated	NA
Hypertension	1.96 (1.59-2.43)	<0.001			Eliminated	NA
Multivessel coronary disease	1.75 (1.41-2.18)	<0.001			Eliminated	NA
Potent $P2Y_{12}$ inhibitor at discharge	0.66 (0.46-0.95)	0.024			Eliminated	NA
High-intensity statin at discharge	1.15 (0.91-1.46)	0.247			Eliminated	NA
Beta-blocker at discharge	0.74 (0.57-0.95)	0.018			Eliminated	NA

*Adjusted for age, sex, and LDL-C level. †Adjusted for age; sex; body mass index; STEMI diagnosis; Killip class; heart rate; systolic blood pressure; diabetes mellitus; hypertension; anemia; creatinine clearance; left ventricular ejection fraction; LDL-C level; high sensitivity C-reactive protein; current smoker status; previous cerebrovascular accident; left anterior descending artery stenosis; multivessel coronary disease; preprocedural TIMI flow grade 0; high-intensity statin at discharge; potent $P2Y_{12}$ inhibitor at discharge; renin-angiotensin-aldosterone system blockers at discharge; and beta-blocker at discharge. Cox regression analysis was performed using the backward elimination selection. AMI, acute myocardial infarction; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; LDL-C, low-density lipoprotein cholesterol; NA, not applicable; STEMI, ST-segment elevation myocardial infarction; TIMI, Thrombolysis In Myocardial Infarction.

Table S6. Results of Cox regression analysis applied to assess the correlates of 3-point major adverse cardiovascular event (3P-MACE) in patients receiving drug-eluting stents implantation (n = 4967).

	Hazard Ratio (95% Confidence Interval)					
	No Adjustment	**P value**	**Model 1***	**P value**	**Model 2†**	**P value**
Age, years	1.05 (1.05-1.06)	<0.001	1.05 (1.04-1.06)	<0.001	1.04 (1.03-1.05)	<0.001
Left ventricular ejection fraction, %	0.97 (0.96-0.97)	<0.001			0.98 (0.98-0.99)	<0.001
LDL-C <70 mg/dL	2.22 (1.75-2.81)	<0.001	1.70 (1.34-2.17)	<0.001	1.40 (1.10-1.79)	0.007
LDL-C 70−99 mg/dL	1.24 (1.02-1.51)	0.029	1.09 (0.90-1.32)	0.396	1.01 (0.83-1.22)	0.953
Previous cerebrovascular accident	2.25 (1.73-2.92)	<0.001			1.48 (1.13-1.92)	0.004
Diabetes mellitus	1.88 (1.59-2.22)	<0.001			1.44 (1.22-1.71)	<0.001
Anemia	2.40 (2.03-2.83)	<0.001			1.43 (1.19-1.67)	<0.001
High-sensitivity C-reactive protein >2mg/dL	1.80 (1.53-2.12)	<0.001			1.41 (1.19-1.67)	<0.001
Killip class >I	1.94 (1.64-2.31)	<0.001			1.35 (1.13-1.62)	0.001
eGFR (CKD-EPI) <60 mL/min/1.73 m^2	2.03 (1.72-2.39)	<0.001			1.31 (1.11-1.56)	0.002
Left anterior descending artery stenosis	1.47 (1.20-1.81)	<0.001			1.27 (1.04-1.57)	0.022
Current smoker	0.63 (0.54-0.75)	<0.001			1.19 (0.99-1.44)	0.069
Preprocedural TIMI flow 0	0.74 (0.63-0.87)	<0.001			0.82 (0.69-0.97)	0.020
Male sex	0.61 (0.51-0.72)	<0.001	1.00 (0.83-1.20)	0.984	Eliminated	NA

Body mass index > 25 kg/m^2	0.68 (0.57-0.81)	<0.001			Eliminated	NA
STEMI diagnosis	0.77 (0.65-0.90)	0.001			Eliminated	NA
Systolic blood pressure <100 mmHg	1.10 (0.82-1.48)	0.508			Eliminated	NA
Heart rate >100 beats/minute	1.67 (1.31-2.12)	<0.001			Eliminated	NA
Hypertension	1.53 (1.30-1.80)	<0.001			Eliminated	NA
Multivessel coronary disease	1.57 (1.32-1.86)	<0.001			Eliminated	NA
Potent $P2Y_{12}$ inhibitor at discharge	0.68 (0.51-0.90)	0.007			Eliminated	NA
High-intensity statin at discharge	1.05 (0.87-1.28)	0.598			Eliminated	NA
Renin-angiotensin-aldosterone system blocker at discharge	0.82 (0.68-0.99)	0.036			Eliminated	NA
Beta-blocker at discharge	0.81 (0.66-0.99)	0.041			Eliminated	NA

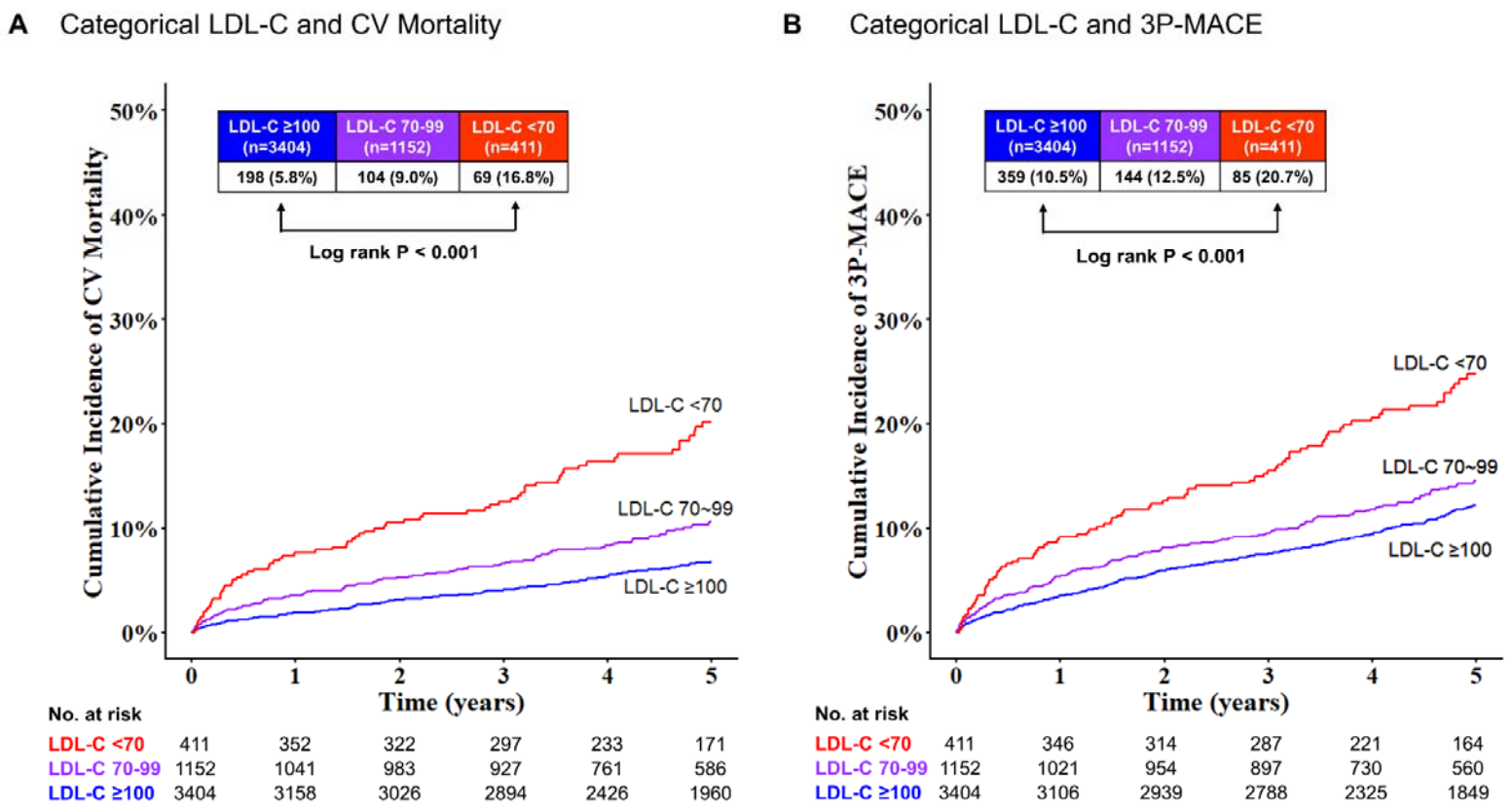
*Adjusted for age, sex, and LDL-C level. †Adjusted for age; sex; body mass index; STEMI diagnosis; Killip class; heart rate; systolic blood pressure; diabetes mellitus; hypertension; anemia; creatinine clearance; left ventricular ejection fraction; LDL-C level; high sensitivity C-reactive protein; current smoker status; previous cerebrovascular accident; left anterior descending artery stenosis; multivessel coronary disease; preprocedural TIMI flow grade 0; high-intensity statin at discharge; potent $P2Y_{12}$ inhibitor at discharge; renin-angiotensin-aldosterone system blockers at discharge; and beta-blocker at discharge. Cox regression analysis was performed using the backward elimination selection. AMI, acute myocardial infarction; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; LDL-C, low-density lipoprotein cholesterol; NA, not applicable; STEMI, ST-segment elevation myocardial infarction; TIMI, Thrombolysis In Myocardial Infarction.

Table S7. Clinical outcomes according to baseline low-density lipoprotein cholesterol (LDL-C) strata in statin non-adherent patients.

	Overall (n=1769)	**LDL-C ≥100 (n=997)**	**LDL-C 70–99 (n=542)**	**LDL-C <70 (n=230)**	**P value***	**P-trend†**
Cardiovascular death	265 (15.0%)	134 (13.4%)	81 (14.9%)	50 (21.7%)	0.006	0.004
Non-fatal myocardial infarction	91 (5.1%)	50 (5.0%)	29 (5.4%)	12 (5.2%)	0.959	0.826
Non-fatal cerebrovascular accident	87 (4.9%)	50 (5.0%)	23 (4.2%)	14 (6.1%)	0.544	0.790
Three-point MACE	368 (20.8%)	194 (19.5%)	115 (21.2%)	59 (25.7%)	0.109	0.043

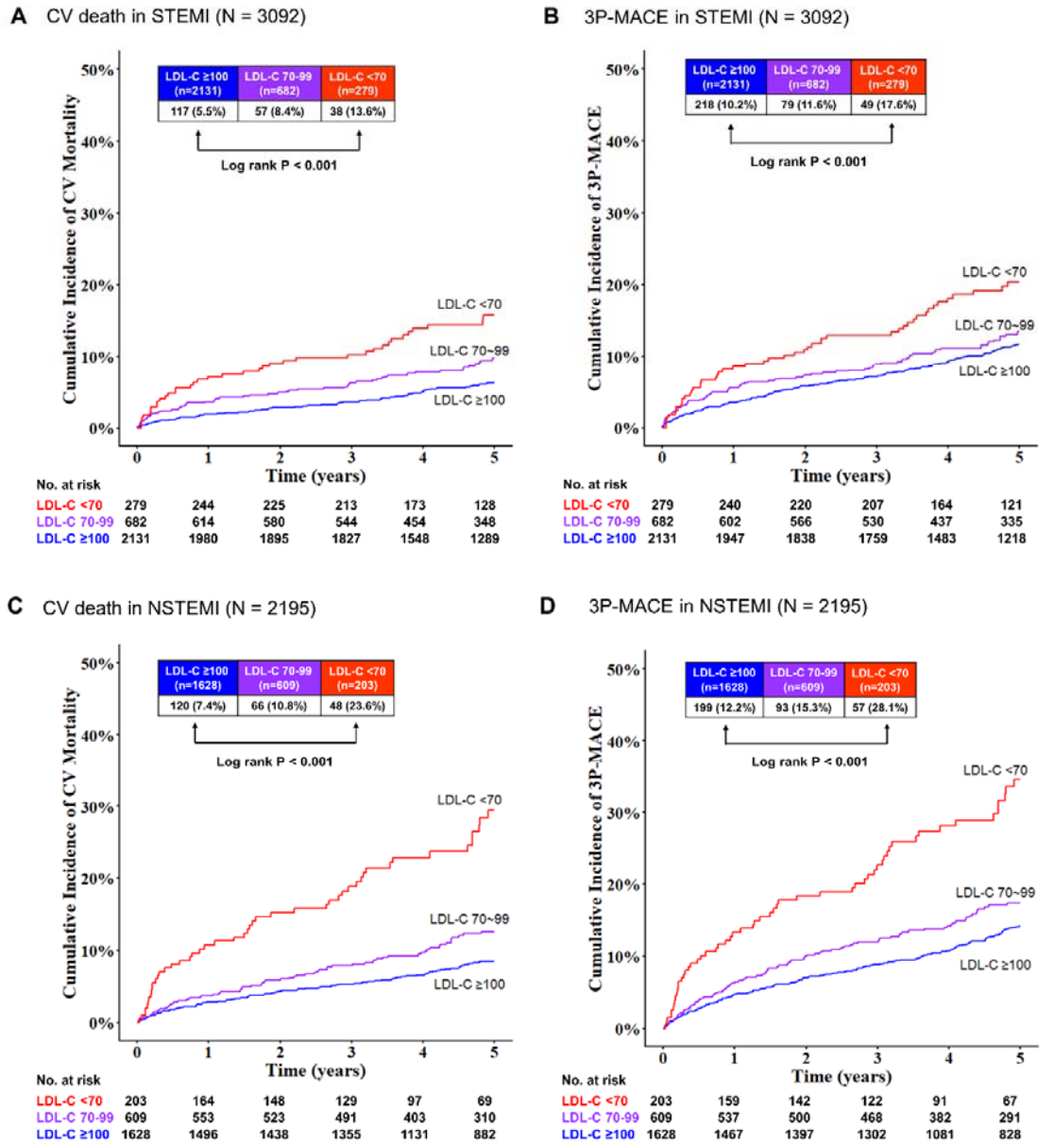
Values are presented as the number (%). *P values are derived from the chi-square test or Fisher's exact test, as appropriate, for between-group comparisons. †P values are calculated for linear trends across the groups. MACE, major adverse cardiocerebrovascular event.

Figure S1. Categorical low-density lipoprotein cholesterol (LDL-C) levels and cardiovascular (CV) outcomes in patients receiving drug-eluting stents implantation (N = 4967).



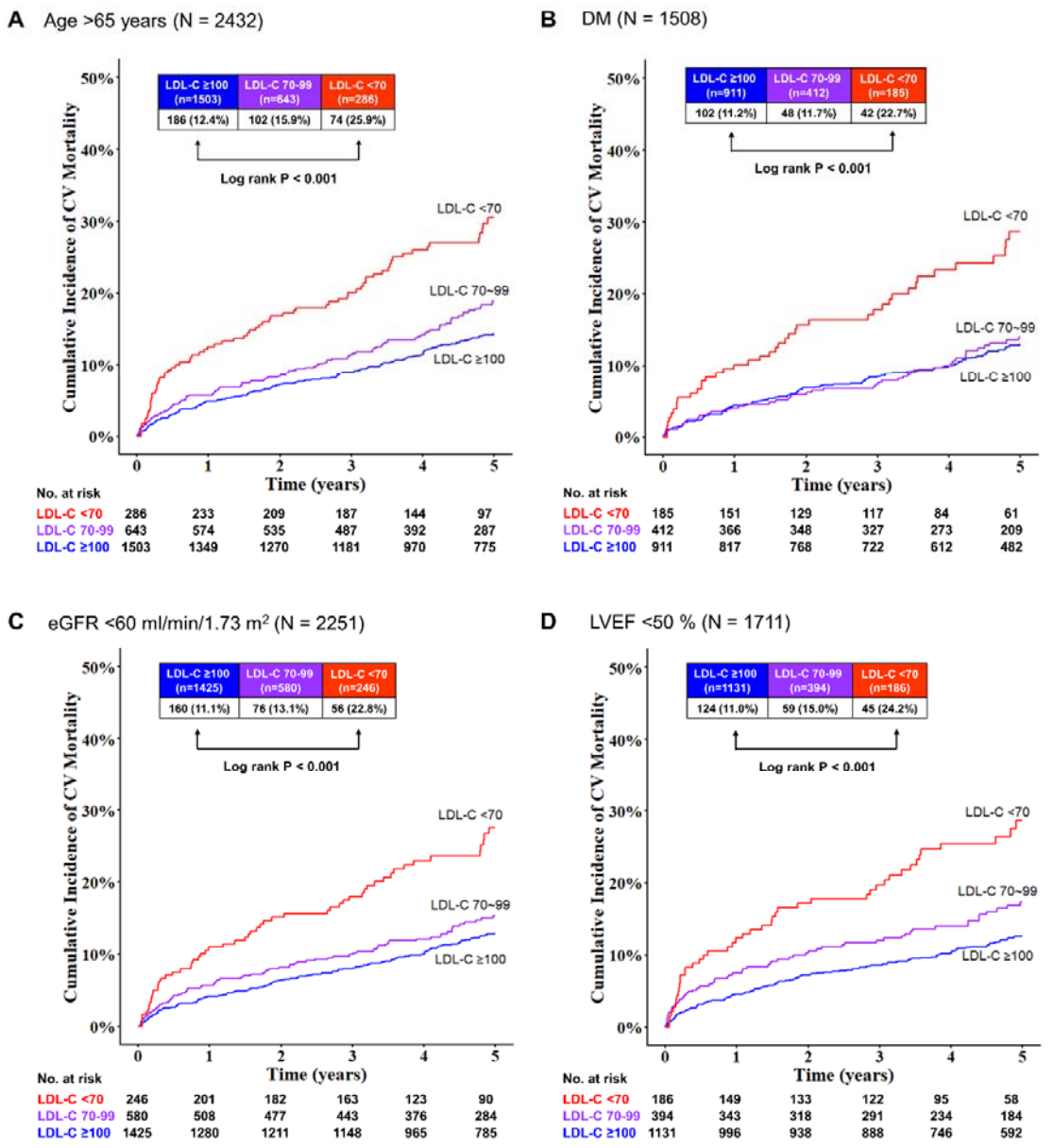
Kaplan-Meier curves for (A.) CV mortality and (B.) 3-point major adverse cardiovascular event (3P-MACE) over 5 years in patients receiving drug-eluting stents implantation are shown.

Figure S2. Categorical low-density lipoprotein cholesterol (LDL-C) levels and cardiovascular (CV) outcomes in patients with ST-segment elevation myocardial infarction (STEMI) or non-ST-segment elevation myocardial infarction (NSTEMI).



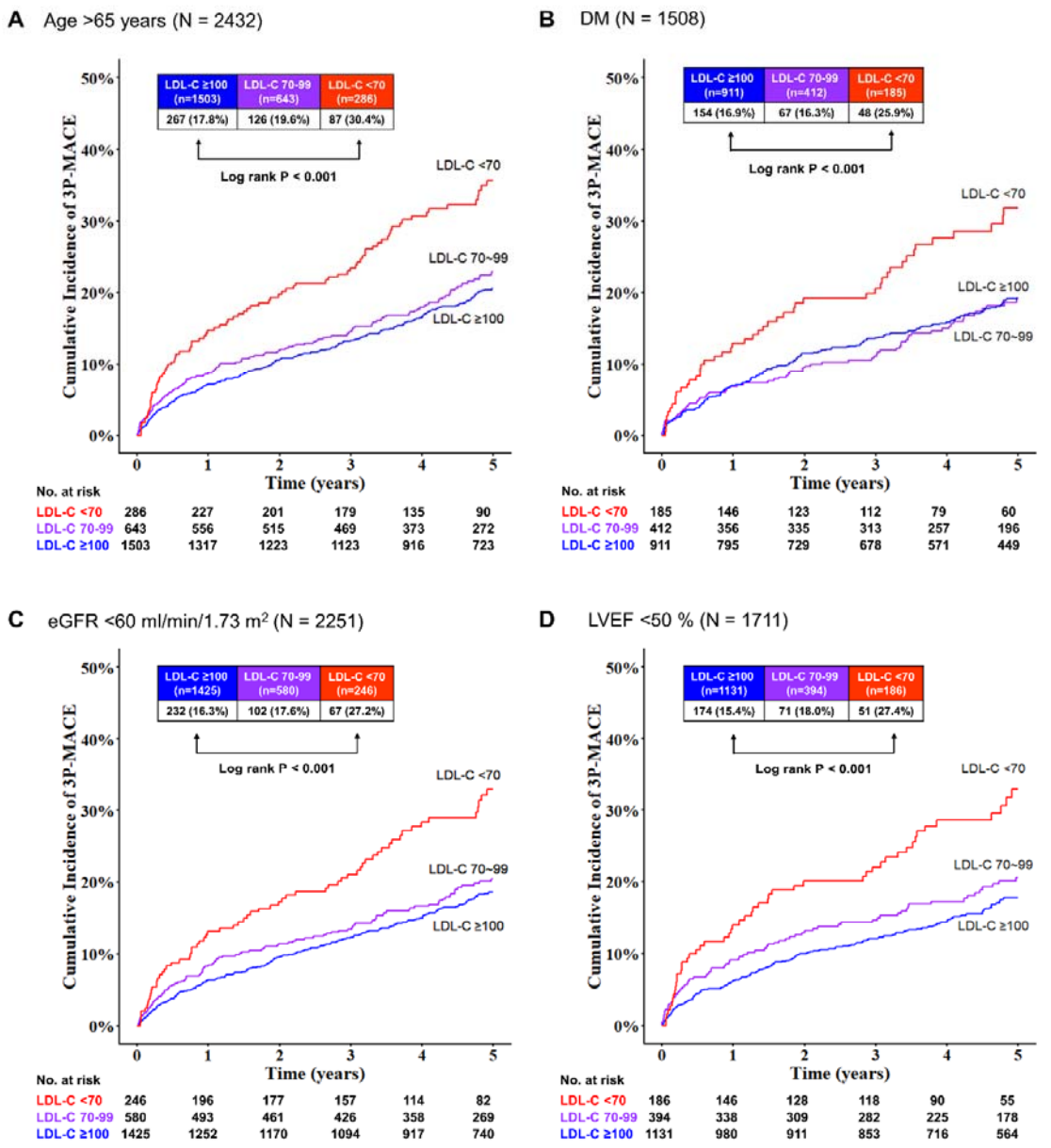
Kaplan-Meier curves for CV mortality and 3-point major adverse cardiovascular events (3P-MACEs) over 5 years stratified by STEMI or NSTEMI are shown. A. CV mortality according to low-density lipoprotein cholesterol (LDL-C) strata in patients with STEMI. B. Three-point MACE according to LDL-C strata in patients with STEMI. C. CV mortality according to LDL-C strata in patients with NSTEMI. B. Three-point MACE according to LDL-C strata in patients with NSTEMI.

Figure S3. Categorical low-density lipoprotein cholesterol (LDL-C) levels and cardiovascular (CV) mortality in diverse high-risk subpopulations.



Kaplan-Meier curves for CV mortality over 5 years in diverse high-risk subpopulations are shown. A. Older adults patients (age ≥65 years), B. diabetes mellitus (DM), C. low estimated glomerular filtration rate (eGFR <60 mL/min/1.73 m^2), and D. low left ventricular ejection fraction (LVEF <50%).

Figure S4. Categorical low-density lipoprotein cholesterol (LDL-C) levels and 3-point major adverse cardiovascular event (3P-MACE) in diverse high-risk subpopulations.



Kaplan-Meier curves for 3P-MACE over 5 years in diverse high-risk subpopulations are shown. A. Older adults patients (age ≥65 years), B. diabetes mellitus (DM), C. low estimated glomerular filtration rate (eGFR <60 mL/min/1.73 m^2), and D. low left ventricular ejection fraction (LVEF <50%).