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Low-density lipoprotein cholesterol levels and adverse clinical outcomes in chronic kidney disease: Results from the KNOW-CKD

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Abstract *Background and aims:* The optimal low-density lipoprotein cholesterol (LDL-C) level to prevent cardiovascular disease in chronic kidney disease (CKD) patients remains unknown. This study aimed to explore the association of LDL-C levels with adverse cardiovascular and kidney outcomes in Korean CKD patients and determine the validity of "the lower, the better" strategy for statin intake.

Methods and results: A total of 1886 patients from the KoreaN cohort study for Outcome in patients With CKD (KNOW-CKD) were included. Patients were classified into four LDL-C categories: <70, 70–99, 100–129, and ≥130 mg/dL. The primary outcome was extended major adverse cardiovascular events (eMACEs). Secondary outcomes included all-cause mortality, and CKD progression.

During the follow-up period, the primary outcome events occurred in 136 (7.2%) patients (16.9 per 1000 person-years). There was a graded association between LDL-C and the risk of eMACEs. The hazard ratios (95% confidence intervals) for LDL-C categories of 70–99, 100–129, and ≥130 mg/dL were 2.06 (1.14–3.73), 2.79 (1.18–6.58), and 4.10 (1.17–14.3), respectively, compared

Abbreviations: ASCVD, Atherosclerotic cardiovascular disease; AUC, Area under the receiver-operating characteristics curves; BMI, Body mass index; CAD, Coronary artery disease; CI, Confidence intervals; CKD, Chronic kidney disease; CVD, Cardiovascular disease; CVE, Cardiovascular event; DM, Diabetes mellitus; eGFR, estimated glomerular filtration rate; ESA, European Atheroscloerosis Society; ESKD, End-stage kidney disease; HDL-C, high-density lipoprotein cholesterol; HR, Hazard ration; hs-CRP, high sensitivity C-reactive protein; IDI, Integrated discrimination improvement; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular events; NRI, Net reclassification improvement; RASB, renin-angiotensin system blocker; RCT, randomized controlled trial; SHARP, Study of Heart and Renal Protection; uACR, urine albumin-creatinine ration; uPCR, urine protein-creatinine ratio.

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to LDL-C <70 mg/dL. Time-varying analysis showed consistent findings. The predictive performance of LDL-C for eMACEs was affected by kidney function. Higher LDL-C levels were also associated with significantly higher risks of CKD progression. However, LDL-C level was not associated with all-cause mortality.
Conclusions: This study showed a graded relationship between LDL-C and the risk of adverse cardiovascular outcome in CKD patients. The lowest risk was observed with LDL-C <70 mg/dL, suggesting that a lower LDL-C target may be acceptable.

Introduction

Low-density lipoprotein cholesterol (LDL-C) plays a major role in atherosclerosis. Cholesterol-lowering therapies can have protective effects on the cardiovascular system [1–3]. Notably, recent trials with proprotein convertase subtilisin/kexin type 9 inhibitors have shown that lowering LDL-C to <50 mg/dL reduces major adverse cardiovascular events (MACEs) in patients with high cardiovascular risk who receive maximal statin therapy [4,5]. The success of these studies has established the so-called "the lower, the better" rule for treating hyperlipidemia in individuals at high risk for atherosclerotic events. However, most interventional studies have been conducted on patients without kidney disease. Studies on patients with end-stage kidney disease (ESKD) failed to show any significant benefits of statin therapy [6–9]. In contrast, the Study of Heart and Renal Protection (SHARP) trial showed that simvastatin/ezetimibe treatment significantly reduced atherosclerotic events in patients with advanced CKD [10]. Therefore, the 2013 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend the use of statin with or without ezetimibe in CKD patients aged ≥50 years [11]. However, the guidelines do not specify the target LDL-C reduction. Very few studies have explored the optimal target level of LDL-C to prevent cardiovascular disease (CVD) in CKD patients. Recently, the European Atherosclerosis Society (EAS) guidelines suggest a LDL-C target <55 mg/dL for prevention of primary or secondary CVD because CKD G4 is considered a very high risk of CVD. For CKD G3 which is also categorized as a high risk, the target is <70 mg/dL [12]. However, to date, the beneficial effects of these targets of LDL-C have not yet been tested in patients with CKD through randomized controlled trials (RCTs). On the other hand, it is also uncertain whether the lower LDL-C target is associated with the slower progression of CKD. Studies on this issue are mostly based on post-hoc analyses of major RCTs and analyses of observational data [13–15] although two small group RCTs have shown possible benefits of statin-based therapy on adverse kidney outcomes in patients with CKD [16,17]. Therefore, whether the "the lower, the better" strategy for individuals without kidney disease could also be effective for these patients is currently unknown.

Hence, we investigated the optimal LDL-C level associated with the lowest risk of the comprehensive composite outcome of non-fatal cardiovascular events or cardiac death in Korean patients with CKD. We also examined whether a similar association could exist for the progression of CKD.

Methods

Study population

The KoreaN cohort study for Outcome in patients With Chronic Kidney Disease (KNOW-CKD) is an ongoing, nationwide, multicenter prospective cohort study. The detailed design and methods of the KNOW-CKD have been previously published (NCT01630486 at http://www.clinicaltrials.gov) [18,19]. Between 2011 and 2016, nine tertiary care hospitals across the nation enrolled a total of 2238 patients who were aged 20–75 years and had CKD G1–G5 without kidney replacement therapy. All enrollments were done at outpatient clinics. The study observation for the occurrence of events closed on March 31, 2019. We excluded 290 patients whose LDL-C data were unavailable or those with missing laboratory and demographic data at baseline. Additionally, 62 patients who dropped out soon after the baseline visit were excluded because information on outcome events was unavailable. Thus, 1886 patients were included (Supplementary Fig. 1).

Data collection

Demographic details on age, sex, smoking status, medical history, and comorbid diseases were obtained from the KNOW-CKD database. Information on economic status, educational level, smoking status, and alcohol consumption was collected at baseline using a questionnaire. Smoking status was classified as never, former, or current. Anthropometric data, including height and weight, were collected at enrollment. Information on medication included the use of renin-angiotensin system blockers (RASBs), anti-platelet drugs, anti-coagulants, phosphorus binders, oral iron, erythropoiesis stimulating agents, active vitamin D, fibrate, ezetimibe, and statins. Types of statins were classified into high-, moderate-, and low-intensity as

previously suggested [20,21]. Blood pressure was measured using an electronic sphygmomanometer in the sitting position after subjects had been in a relaxed state for at least 5 min. Blood and urine samples were collected after overnight fasting, and aliquots of the samples were sent to the central laboratory (Lab Genomics, Seongnam, Korea) for measurement of serum creatinine and proteinuria. We measured the creatinine levels using a calibrated traceable isotope dilution mass spectrometer and calculated the estimated glomerular filtration rate (eGFR) using the CKD Epidemiologic Collaboration equation [22]. The urine albumin-to-creatinine ratio (uACR) was calculated as urine albumin concentration divided by urine creatinine concentration (mg/g). In each individual participating center, the following laboratory parameters were measured at baseline and annually thereafter: complete blood cell count, fasting glucose, blood urea nitrogen, albumin, calcium, and phosphorus. High sensitivity C-reactive protein (hs-CRP) and lipid profiles for total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-C), and LDL-C were measured at baseline and at 1, 3, and 7 years. Lipid profiles were measured by the direct enzyme method at the local laboratory of each participating center. Detailed information on the analyzer was provided in Supplemental materials.

Exposure and outcome ascertainment

The main predictor of this study was LDL-C level. To examine the association between LDL-C and adverse outcomes, patients were classified into four LDL-C categories of $<$70, 70–99, 100–129, and $\geq$130 mg/dL.

The primary outcome of interest was a composite of eMACEs, which was defined as the first occurrence of nonfatal cardiovascular events (CVEs) or cardiovascular death during follow-up. Nonfatal CVEs included any nonfatal coronary artery events (unstable angina, myocardial infarction, or coronary intervention/surgery), hospitalization for heart failure, or cerebrovascular events (ischemic or hemorrhagic stroke, or carotid intervention). Cardiovascular deaths included death that resulted from acute myocardial infarction, sudden cardiac death, death due to heart failure, and death due to stroke [23]. The secondary endpoints included death from any cause and CKD progression. CKD progression was defined as a composite CKD outcome of $\geq$50% decline in eGFR during follow-up or onset of ESKD, including initiation of dialysis or kidney transplantation. All patients had been under close observation for the occurrence of events, and patients who reached the endpoints were reported by each center.

Statistical analysis

Continuous variables with normal distribution are expressed as mean with standard deviation, and those with skewed distribution are described as median with interquartile range. The Shapiro–Wilk normality test was used for normality testing. Categorical variables are presented as numbers and percentages. The one-way analysis of variance was used for normally distributed data, and the Kruskal–Wallis test was used for skewed data to identify differences and compare the clinical characteristics between groups.

To examine the association between LDL-C levels and the risk of primary and secondary outcomes, we performed a conventional Cox proportional hazard regression model and a time-varying model in which time-dependent covariates were considered [24]. Conventional models with baseline values were constructed to ascertain the association of long-term exposure with adverse outcome. Time-varying models were used to account for changes in LDL-C over time and to ascertain their short-term effect between intervals of measurements. In the time-varying analyses, all laboratory data, systolic blood pressure (SBP), body mass index (BMI), and medication status were incorporated as time-dependent variables. Variables that had statistical significance in the univariate analysis (Supplementary Table 1) and conventional factors that are known to influence cardiovascular risk were included in the multivariable models. For each analysis, three models were constructed based on the level of multivariate adjustment. Model 1 included age, sex, study center, history of CVD, diabetes mellitus (DM), smoking status, alcohol consumption status, socioeconomic status, education status, BMI, SBP, serum albumin, HDL-C, triglyceride, serum phosphate, and hs-CRP. Model 2 included eGFR and uACR in addition to the variables in model 1. Further adjustments were made for concurrent medications, such as renin-angiotensin system blockers (RASBs), type of statins, fibrates, and ezetimibe, in model 3.

Proportional hazards assumptions were confirmed using Schoenfeld residuals. The Kaplan–Meier curve analysis for the study outcomes was employed to derive survival rates, and between-group differences were compared by a log-rank test. Survival was defined as the time interval between the baseline measurements and the first onset of outcome events. Patients lost to follow-up were censored at the date of their last examination. For analysis with kidney outcome, we constructed a cause-specific hazard model, in which death that occurred before reaching the kidney outcome was treated as a competing risk and considered a censored event.

To test the robustness of the association between LDL-C and risk of eMACEs, we performed two sensitivity analyses in 1623 patients after excluding 263 patients with a history of CVD (myocardial infarction, heart failure, CAD, stroke, peripheral artery disease) and in quartile groups of LDL-C levels. To compare the predictive ability of LDL-C, we calculated the c-statistics, area under the receiver-operating characteristics curves (AUCs), category-free net reclassification improvement (NRI), and integrated discrimination improvement (IDI) for models. Thus, we constructed the base and LDL-C models. The base model included risk factors for eMACEs, including age, sex, CVD, DM, smoking status, alcohol status, socioeconomic status, education status, BMI, SBP, serum albumin, HDL-C, triglyceride, serum phosphate, hs-CRP, eGFR, uACR, RASBs, type of statins, fibrates, and ezetimibe. The LDL-C model

was then constructed after adding LDL-C to the base model. Furthermore, we compared prediction indices stratified by eGFR (<60 and ≥60 mL/min/1.73 m^2).

The results are expressed as hazard ratios (HRs) and 95% confidence intervals (CIs). Data were analyzed using STATA software version 15.1 (StataCorp, College Station, TX, USA). A p-value of <0.05 was considered statistically significant.

Ethics statement

All procedures were performed in accordance with the ethical standards of the respective institutional and national research committees (IRB approval number: H-1104-089-359). The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved priorly by the institutional review board of each participating clinical center. All study participants provided written informed consent.

Results

Baseline characteristics

The demographic, clinical, and laboratory characteristics of the patients are presented in Table 1. Among 1886 participants, the mean age was 53.6 ± 12.2 years, and the mean LDL-C level was 97.1 ± 31.5 mg/dL. Patients with lower LDL-C level were older, more likely to be male, current smokers, and had more comorbid conditions. In contrast, patients with higher LDL-C levels had proteinuria and higher inflammation levels (Table 1, Supplementary Tables 2 and 3).

LDL-C and risk of the primary outcome

During a follow-up of 8033 person-years (median of 5.2 years), the primary composite outcome of eMACEs occurred in 136 patients (7.2%). There were 23 (6.2%), 56 (8.0%), 40 (7.5%), and 17 (6.1%) events among patients with baseline LDL-C level of <70, 70–99, 100–129, and ≥130 mg/dL, respectively (Supplementary Table 4). The corresponding incidence rates of eMACEs for each LDL-C category were 15.2, 18.4, 17.2, and 14.7 per 1000 person-years, respectively. In the multivariable Cox model after adjustment of confounding factors, a graded association of LDL-C level with risk of the primary outcome was found (Table 2 and Fig. 1A). The final model showed that the HRs (95% CI) for LDL-C categories 70–99, 100–129, and ≥130 mg/dL were 2.06 (1.14–3.73), 2.79 (1.18–6.58), and 4.10 (1.17–14.3), respectively, compared with LDL-C of <70 mg/dL (model 3). The adjusted cumulative eMACEs were also significantly higher in patients with higher LDL-C level than in those with a lower LDL-C level (Fig. 2A). Because LDL-C and other lipid levels changed over time during the follow up period (Supplementary Table 5), we constructed time-varying model. This association was consistent in the time-varying model. Patients with time-updated LDL-C of 70–99, 100–129, and ≥130 mg/dL had a 2.12-, 3.42-, and 4.88-fold higher risk of eMACEs than those with LDL-C of <70 mg/dL (Table 2 and Fig. 1B).

In analyses with LDL-C as a continuous variable, each 30 mg/dL LDL-C increment was associated with 59% higher risk for eMACE development and these finding was similar in the time-varying model.

Secondary outcome analyses

We further analyzed the association of LDL-C with secondary outcomes. In the analysis for all-cause mortality, 97 (5.1%) deaths from any cause occurred during follow-up. However, there was no significant difference in the risk of all-cause mortality across the LDL-C categories (Table 3, Supplementary Table 6, and Fig. 2B).

Finally, we analyzed the association between LDL-C levels and adverse kidney outcome. During follow-up, a total of 596 (31.6%) patients developed composite kidney outcome events. Similar to the primary analyses, higher LDL-C levels were associated with a significantly higher risk of adverse kidney outcome (Table 3, Supplementary Table 7, and Fig. 2C). In the multivariable-adjusted Cox model, the HRs (95% CI) for each LDL-C category were 1.28 (1.00–1.66), 1.79 (1.22–2.61), and 2.21 (1.27–3.85), respectively, compared to those with LDL-C of <70 mg/dL. In the time-varying model, the corresponding HRs were 1.29 (0.99–1.69), 1.79 (1.23–2.62), and 2.05 (1.19–3.56), respectively (Table 3 and Supplementary Table 7).

Sensitivity analysis

A sensitivity analysis after excluding 263 patients with a history of CVD showed consistent findings. In the baseline LDL-C model, patients with LDL-C levels of 70–99, 100–129, and ≥130 mg/dL had a 3.22- (1.16–8.97), 3.66- (0.96–13.9), and 6.20-fold (1.02–37.2) higher risk of eMACEs, respectively, compared with individuals with LDL-C of <70 mg/dL. The time-varying model yielded similar results (Supplementary Table 8).

Furthermore, in another sensitivity analysis with quartile groups of LDL-C levels, there was a graded association between LDL-C and the primary outcome. The HRs for the 2nd, 3rd, and highest quartile of LDL-C were 2.07 (95% CI, 1.17–3.67), 1.96 (95% CI, 0.95–4.06), and 3.59 (1.31–9.89), respectively, compared with the lowest quartile (Supplementary Table 9).

Predictive performance of LDL-C

The predictive performance of LDL-C for the primary outcome was tested by comparing AUC, c-statistics, NRI, and IDI (Supplementary Table 10 and Supplementary Fig. 2). The AUC and c-statistic for the base model were 0.761 (0.722–0.800) and 0.790 (0.754–0.826), respectively. Adding LDL-C to the base model did not improve these indices. These findings suggest that the predictive ability of LDL-C was not greater than that of conventional factors.

Table 1 Baseline characteristics of patients according to the LDL-C group.

	Total (n = 1886)	LDL-C group				p
		<70 mg/dL (n = 369)	70–99 mg/dL (n = 701)	100–129 mg/dL (n = 536)	≥130 mg/dL (n = 280)	
Demographic data						
Age (years)	53.6 ± 12.2	55.4 ± 11.9	54.4 ± 12.2	52.8 ± 11.8	50.9 ± 13.1	<0.01
Sex (female, %)	744 (39.4%)	123 (33.3%)	275 (39.2%)	229 (42.7%)	117 (41.8%)	0.03
BMI (kg/m^2)	24.5 ± 3.4	24.5 ± 3.2	24.4 ± 3.3	24.5 ± 3.4	24.9 ± 3.8	0.20
SBP (mmHg)	127.8 ± 16.1	126.7 ± 14.6	128.0 ± 16.5	128.4 ± 16.2	127.7 ± 16.6	0.44
Economic status						0.09
≥$4905/month	428 (22.7%)	76 (20.6%)	180 (25.7%)	119 (22.2%)	53 (18.9%)	
$1635–4905/month	979 (51.9%)	199 (53.9%)	334 (47.6%)	285 (53.2%)	161 (57.5%)	
<$1635/month	479 (25.4%)	94 (25.5%)	187 (26.7%)	132 (24.6%)	66 (23.6%)	
Education						0.51
<9 years	466 (24.7%)	95 (25.7%)	172 (24.5%)	133 (24.8%)	66 (23.6%)	
9–12 years	655 (34.7%)	132 (35.8%)	231 (33.0%)	181 (33.8%)	111 (39.6%)	
≥12 years	765 (40.6%)	142 (38.5%)	298 (42.5%)	222 (41.4%)	103 (36.8%)	
Smoking status						0.02
Never	1005 (53.3%)	178 (48.2%)	363 (51.8%)	307 (57.3%)	157 (56.1%)	
Former	577 (30.6%)	120 (32.5%)	238 (34.0%)	144 (26.9%)	75 (26.8%)	
Current	304 (16.1%)	71 (19.2%)	100 (14.3%)	85 (15.9%)	48 (17.1%)	
Alcohol intake						0.70
Mild (none or <1 g/day)	1482 (78.6%)	287 (77.8%)	560 (79.9%)	421 (78.5%)	214 (76.4%)	
Moderate (1–19 g/day)	189 (10.0%)	35 (9.5%)	62 (8.8%)	59 (11.0%)	33 (11.8%)	
High (≥20 g/day)	215 (11.4%)	47 (12.7%)	79 (11.3%)	56 (10.4%)	33 (11.8%)	
Comorbidities						
Hypertension	1817 (96.3%)	358 (97.0%)	673 (96.0%)	516 (96.3%)	270 (96.4%)	0.87
Diabetes	635 (33.7%)	159 (43.1%)	254 (36.2%)	148 (27.6%)	74 (26.4%)	<0.01
Coronary artery disease	113 (6.0%)	40 (10.8%)	38 (5.4%)	27 (5.0%)	8 (2.9%)	<0.01
Myocardial infarction	31 (1.6%)	13 (3.5%)	8 (1.1%)	9 (1.7%)	1 (0.4%)	<0.01
Peripheral vascular disease	70 (3.7%)	21 (5.7%)	25 (3.6%)	17 (3.2%)	7 (2.5%)	0.13
Stroke	111 (5.9%)	28 (7.6%)	54 (7.7%)	21 (3.9%)	8 (2.9%)	<0.01
Congestive heart failure	28 (1.5%)	11 (3.0%)	6 (0.9%)	8 (1.5%)	3 (1.1%)	0.05
Charlson comorbidity index	2.3 ± 1.6	2.7 ± 1.5	2.4 ± 1.6	2.0 ± 1.6	1.9 ± 1.6	<0.01
Primary renal disease						<0.01
Diabetic nephropathy	474 (25.1%)	124 (33.6%)	187 (26.7%)	113 (21.1%)	50 (17.9%)	
Hypertensive kidney disease	360 (19.1%)	72 (19.5%)	139 (19.8%)	92 (17.2%)	57 (20.4%)	
Glomerulonephritis	596 (31.6%)	98 (26.6%)	223 (31.8%)	164 (30.6%)	111 (39.6%)	
Polycystic kidney disease	324 (17.2%)	40 (10.8%)	115 (16.4%)	126 (23.5%)	43 (15.4%)	
Others	132 (7.0%)	35 (9.5%)	37 (5.3%)	41 (7.6%)	19 (6.8%)	
Medication						
Anti-platelet drugs	561 (29.7%)	142 (38.5%)	217 (31.0%)	132 (24.6%)	70 (25.0%)	<0.01
Warfarin	24 (1.3%)	4 (1.1%)	9 (1.3%)	6 (1.1%)	5 (1.8%)	0.85
Phosphate binder	158 (8.4%)	41 (11.1%)	61 (8.7%)	38 (7.1%)	18 (6.4%)	0.10
Active Vitamin D	42 (2.2%)	5 (1.4%)	17 (2.4%)	14 (2.6%)	6 (2.1%)	0.62
Oral iron	267 (14.2%)	63 (17.1%)	114 (16.3%)	53 (9.9%)	37 (13.2%)	<0.01
Erythropoiesis stimulating agents	140 (7.4%)	37 (10.0%)	59 (8.4%)	31 (5.8%)	13 (4.6%)	0.02
RASBs	1619 (85.8%)	317 (85.9%)	603 (86.0%)	461 (86.0%)	238 (85.0%)	0.98
Fibrate	52 (2.8%)	12 (3.3%)	21 (3.0%)	15 (2.8%)	4 (1.4%)	0.51
Ezetimibe	121 (6.4%)	34 (9.2%)	44 (6.3%)	27 (5.0%)	16 (5.7%)	0.08
Statin						<0.01
No statin	908 (48.1%)	81 (22.0%)	296 (42.2%)	352 (65.7%)	179 (63.9%)	
Low-intensity	349 (18.5%)	79 (21.4%)	144 (20.5%)	85 (15.9%)	41 (14.6%)	
Moderate-intensity	584 (31.0%)	192 (52.0%)	247 (35.2%)	93 (17.4%)	52 (18.6%)	
High-intensity	45 (2.4%)	17 (4.6%)	14 (2.0%)	6 (1.1%)	8 (2.9%)	
Laboratory parameters						
eGFR (mL/min/1.73 m^2)	53.5 ± 30.9	45.8 ± 27.4	51.3 ± 30.0	58.8 ± 31.7	59.4 ± 33.2	<0.01
BUN (mg/dL)	28.0 ± 15.5	30.7 ± 16.8	28.6 ± 15.3	26.3 ± 15.1	26.6 ± 14.5	<0.01
Albumin (g/dL)	4.2 ± 0.4	4.2 ± 0.3	4.2 ± 0.4	4.2 ± 0.4	4.1 ± 0.6	<0.01
hs-CRP (mg/L)	0.6 (0.2–1.7)	0.6 (0.2–1.4)	0.6 (0.2–1.5)	0.7 (0.3–2.0)	0.8 (0.3–1.8)	<0.01
Phosphate (mg/dL)	3.7 ± 0.7	3.7 ± 0.7	3.7 ± 0.7	3.6 ± 0.6	3.7 ± 0.7	0.19
Fasting glucose (mg/dL)	110.1 ± 38.8	110.4 ± 37.5	112.3 ± 44.0	108.8 ± 34.6	106.9 ± 33.5	0.18
Tchol (mg/dL)	174.3 ± 38.8	133.1 ± 22.1	161.2 ± 23.0	190.5 ± 19.0	230.4 ± 34.3	<0.01
HDL-C (mg/dL)	49.6 ± 15.6	46.3 ± 16.5	50.0 ± 16.3	50.5 ± 13.6	50.9 ± 15.5	<0.01
TG (mg/dL)	132.0 (92–193)	128.0 (85–193)	124.0 (85–178)	134.0 (95–193)	155.0 (111–211)	<0.01

Table 1 (*continued*)

	Total (n = 1886)	LDL-C group				p
		<70 mg/dL (n = 369)	70–99 mg/dL (n = 701)	100–129 mg/dL (n = 536)	≥130 mg/dL (n = 280)	
LDL-C (mg/dL)	97.1 ± 31.5	58.0 ± 9.0	84.2 ± 8.5	112.8 ± 8.4	151.0 ± 21.2	<0.01
uPCR (g/g)	0.5 (0.1–1.4)	0.5 (0.2–1.2)	0.5 (0.2–1.6)	0.4 (0.1–1.2)	0.6 (0.1–2.4)	0.05
uACR (mg/g)	341.9 (77–1033)	332.2 (90–932)	371.6 (81–1098)	280.0 (66–877)	474.6 (56–1661)	0.04

Data are presented as means ± standard deviation, numbers (%), or medians and interquartile ranges.
BMI, body mass index; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; SBP, systolic blood pressure; LDL-C, low-density lipoprotein cholesterol; RASBs, renin-angiotensin system blockers; Tchol, total cholesterol; TG, triglyceride; uPCR, urine protein-to-creatinine ratio; uACR, urine albumin-to-creatinine ratio.

Because kidney function can influence the relationship between LDL-C and risk of CVD [25], we tested if the prediction performance of the model with LDL-C differs depending on kidney function. The AUC and c-statistic for the model of eGFR < 60 mL/min/1.73 m^2 were 0.713 (0.675–0.751) and 0.789 (0.749–0.830), respectively. These predictive indices significantly increased in the model of eGFR ≥ 60 mL/min/1.73 m^2, suggesting that the predictive performance of LDL-C for eMACE was affected by kidney function (Supplementary Table 11 and Supplementary Fig. 3).

Discussion

In this study, we identified a graded linear relationship between LDL-C levels and the risk of eMACEs. The magnitude of HR was more elevated as LDL-C levels increased, and patients with LDL-C ≥130 mg/dL had a 4.10-fold higher risk of eMACEs than those with LDL-C <70 mg/dL. The LDL-C level was not associated with all-cause mortality. We found a significantly graded association between the LDL-C level and adverse kidney outcomes. Our findings suggest that "the lower, the better" strategy in the management of hyperlipidemia may be valid in CKD patients without kidney replacement therapy.

LDL-C is a well-known risk factor for the development of future atherosclerotic cardiovascular disease (ASCVD). The importance of reducing LDL-C level to prevent CVD is well-established. Summaries of meta-analyses with a prospective cohort and randomized controlled studies have consistently shown a strong and log-linear relationship between LDL-C level and the risk of ASCVD [26–30].

Table 2 Hazard ratios for the risk of eMACEs according to the LDL-C group.

	Model 1		Model 2		Model 3	
	HR [95% CI]	p	HR [95% CI]	p	HR [95% CI]	p
Baseline LDL-C, mg/dL						
Continuous model, per 30 mg/dL increase	1.64 [1.10–2.43]	0.01	1.62 [1.09–2.40]	0.02	1.59 [1.07–2.37]	0.02
Categorical model						
<70	1.00 [reference]		1.00 [reference]		1.00 [reference]	
70–99	2.14 [1.18–3.87]	0.01	2.11 [1.17–3.82]	0.01	2.06 [1.14–3.73]	0.01
100–129	3.05 [1.30–7.16]	0.01	2.90 [1.24–6.80]	0.01	2.79 [1.18–6.58]	0.02
≥130	4.27 [1.21–15.0]	0.02	4.25 [1.22–14.9]	0.02	4.10 [1.17–14.3]	0.03
Time-varying LDL-C, mg/dL						
Continuous model, per 30 mg/dL increase	1.78 [1.19–2.66]	<0.01	1.79 [1.19–2.67]	<0.01	1.73 [1.15–2.60]	<0.01
Categorical model						
<70	1.00 [reference]		1.00 [reference]		1.00 [reference]	
70–99	2.12 [1.15–3.90]	0.02	2.16 [1.17–3.99]	0.01	2.12 [1.15–3.91]	0.02
100–129	3.67 [1.54–8.76]	<0.01	3.65 [1.53–8.70]	<0.01	3.42 [1.43–8.21]	0.01
≥130	5.01 [1.36–18.4]	0.02	5.26 [1.43–19.3]	0.01	4.88 [1.33–17.9]	0.02

Model 1: adjusted for age, sex, cardiovascular disease (coronary artery disease, myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease), diabetes mellitus, study center, alcohol, smoking status, socioeconomic status, educational status, body mass index, systolic blood pressure, and laboratory parameters (such as serum HDL-C, tryglyceride, high-sensitivity C-reactive protein, serum albumin, and serum phosphate).
Model 2: adjusted for model 1 parameters plus renal parameters such as estimated glomerular filtration rate and urine albumin-to-creatinine ratio.
Model 3: adjusted for model 2 parameters plus the use of medications such as type of statin, fibrate, ezetimibe, and renin-angiotensin system blockers.
CI, confidence interval; eMACEs, extended major cardiovascular events; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.

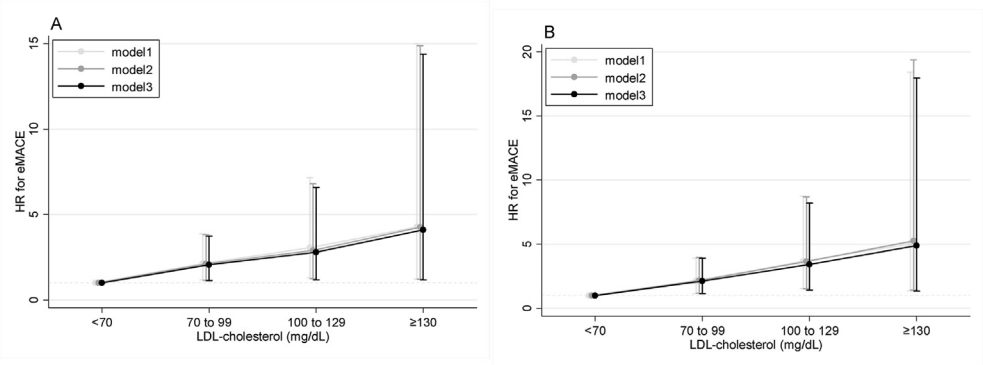

Figure 1 Associations of serum low-density lipoprotein cholesterol (LDL-C) levels with extended major cardiovascular events (eMACEs). (A) Baseline model and (B) time-varying model (hazard ratios and 95% confidence interval [CI] error bars). Model 1: adjusted for age, sex, study center, cardiovascular disease (CVD), diabetes mellitus (DM), alcohol, smoking status, socioeconomic status, educational status, body mass index (BMI), systolic blood pressure (SBP), laboratory parameters, such as serum high-density lipoprotein cholesterol (HDL-C), triglyceride, high-sensitivity C-reactive protein (hs-CRP), serum albumin, and serum phosphate. Model 2: adjusted for model 1 parameters plus renal parameters such as estimated glomerular filtration rate (eGFR) and urine albumin-to-creatinine ratio (uACR). Model 3: adjusted for model 2 parameters plus the use of medications such as type of statin, fibrate, ezetimibe, and renin-angiotensin system blockers (RASBs).

Because CVD is the most common cause of death in CKD patients, the 2018 American College of Cardiology/American Heart Association guidelines define CKD as a risk enhancing factor, and recommend intensity therapy in CKD without kidney replacement therapy patients aged 40–75 years if they have an LDL-C level of 70–189 mg/dL and 10-year ASCVD risk of ≥7.5% [20]. This is more likely to be a treat-to-target approach because the guideline specifically designates target LDL-C reduction by 30%–49% for intermediate-risk patients and ≥50% for high-risk patients.

There is a lack of relevant studies in CKD patients, and a dose-dependent relationship between LDL-C and risk of CVD is uncertain as studies report conflicting results. A post-hoc analysis of the Modification of Diet in Renal Disease study showed no association between lipid variables or cardiovascular mortality in 840 stage G3–4 CKD patients [31]. The Chronic Renal Insufficiency Cohort study investigators also failed to find any significant association between LDL-C levels and risk of ASCVD in 3811 adults with CKD [32]. However, the Alberta Kidney Disease Network study showed that higher LDL-C level were associated with increased risk of myocardial infarction; the HR for LDL-C of ≥160 mg/dL was 2.06 (95% CI, 1.59–2.67) compared to LDL-C of 100–130 mg/dL among patients with eGFR of 15–59.9 mL/min/1.73 m^2 [25]. Similarly, we showed that the risk of eMACEs linearly increased with higher LDL-C levels. This significant association persisted in patients without a prior history of CAD.

Despite a significant relationship between LDL-C and adverse cardiovascular outcomes, the predictive performance of LDL-C was not strong in this study. The AUC of the LDL-C model was 0.768, suggesting that the predictive performance of LDL-C is acceptable, but not excellent [33–35]. This finding can be partly explained by different pathophysiological mechanisms for vascular events in severe kidney failure. Other nontraditional mechanisms, such as inflammation, oxidative stress, uremic toxins, and malnutrition, may contribute more to vascular damage than traditional factors in advanced CKD [36–39]. Alternatively, as kidney failure worsens, the properties of LDL-C change, and other lipids and lipoprotein particles became more atherogenic; thus, the importance of LDL-C levels may be diluted in severe CKD [32,40–44]. Notably, in our study, the prediction performance was greater in the model with better kidney function. In line with our findings, the aforementioned Canadian study [25] also showed that the magnitude of HR for the association between LDL-C and risk of myocardial infarction were greater in individuals with eGFR ≥ 60 mL/min/1.73 m^2 than in those with lower eGFR. The clinical implications of LDL-C may vary depending on kidney function, and this calls for a customized treatment approach based on CKD stages.

In our previous study, statin intensity was not associated with CKD progression [21]. However, in this study, there was a significant association of LDL-C with adverse kidney outcomes. The role of LDL-C in kidney function decline is unknown, and there has been no randomized controlled study with CKD progression specifically as the primary endpoint. Previous meta-analyses of RCTs have shown that lowering LDL-C might attenuate loss of kidney function [45,46]. However, these analyses included patients with mildly decreased kidney function. In contrast, the SHARP study investigators failed to demonstrate the beneficial effects of lowering LDL-C on the progression of CKD in patients with advanced CKD [13]. Cardiac and kidney dysfunction likely share pathophysiologic mechanisms, given the deleterious effects of LDL-C on the vascular system in both organs [30,47].

The strengths of our study include the inclusion of only CKD patients with various kidney function, rigorous adjustment of potential confounding factors, in-depth analyses using baseline and time-varying models. We believe our findings can support the lower target of LDL-C strategy in patients with CKD as suggested by the EAS guideline.

This study has several limitations. First, given the observational nature of the study, a causal relationship could not be determined, and potential confounding

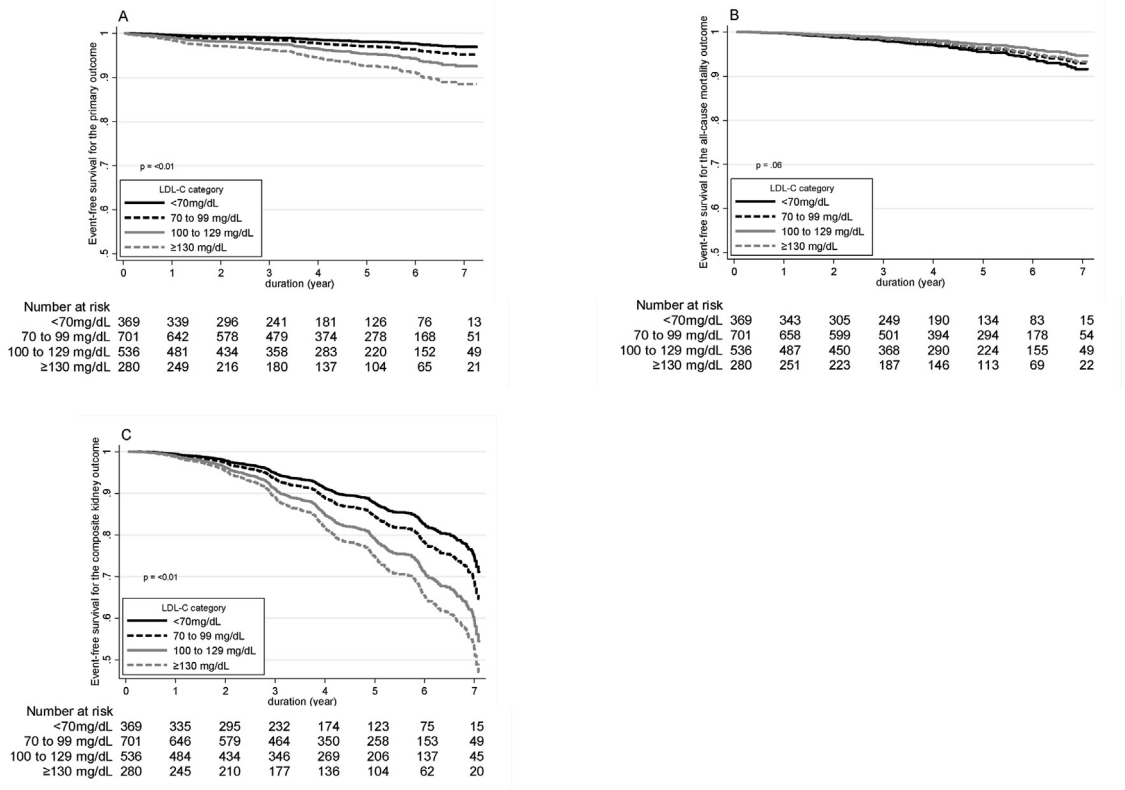

Figure 2 Kaplan–Meier curve for (A) the primary outcome of extended major cardiovascular events (eMACEs), and the individual secondary outcomes of (B) all-cause mortality, and (C) composite kidney outcome events according to the LDL-C group.

Table 3 Hazard ratios for the risk of secondary outcomes according to the LDL-C group.

LDL-C category	All-cause mortality		Composite kidney outcome	
	HR [95% CI]	*p*	HR [95% CI]	*p*
Baseline LDL-C, mg/dL				
<70	1.00 [reference]		1.00 [reference]	
70–99	1.15 [0.61–2.18]	0.67	1.28 [0.99–1.66]	0.06
100–129	0.71 [0.26–1.94]	0.51	1.79 [1.22–2.61]	<0.01
≥130	1.39 [0.31–6.24]	0.69	2.21 [1.27–3.85]	0.01
Time-varying LDL-C, mg/dL				
<70	1.00 [reference]		1.00 [reference]	
70–99	1.34 [0.68–2.62]	0.39	1.29 [0.99–1.69]	0.06
100–129	0.88 [0.32–2.42]	0.81	1.79 [1.23–2.62]	<0.01
≥130	1.21 [0.26–5.61]	0.81	2.05 [1.19–3.56]	0.01

Each model was adjusted for age, sex, cardiovascular disease (coronary artery disease, myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease), diabetes mellitus, study center, alcohol, smoking status, socioeconomic status, educational status, body mass index, systolic blood pressure, laboratory parameters (such as serum HDL-C, tryglyceride, high-sensitivity C-reactive protein, serum albumin, serum phosphate, estimated glomerular filtration rate and urine albumin-to-creatinine ratio), and use of medications (type of statin, fibrate, ezetimibe, and renin-angiotensin system blockers).
CI, confidence interval; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.

factors might not be controlled. The design of our study could not allow us to examine the effects of statins on adverse outcomes. However, we exclusively included CKD patients and sought to address unresolved issues in CKD research. Both conventional Cox and time-varying models with extensive adjustment levels showed consistent results. Second, there was no relationship between LDL-C and all-cause mortality, which is unexpected as CVD is the leading cause of death in CKD patients. However, there were only 97 deaths in our study which could not provide adequate statistical power. The low death rate is a unique feature in our cohort, and in-depth analysis in comparison with other CKD cohorts is under investigation. Third, serum LDL-C was measured at each participating center; precision may vary. However, all laboratories used the same direct enzymatic assay. Fourth, the EAS suggests a target of LDL-C <55 mg/dL in the very high risk group. The association of such lower level of LDL-C with outcome was not feasible because there were only 109 patients in this LDL-C category. Fifth, the graded relationship between LDL-C and adverse outcome was more pronounced after adjustment of confounding factors, raising concern on over-adjustment issue. Notably, there were many differences in baseline characteristics among groups, which might partly explain this phenomenon. We selected factors showing significant association in univariate Cox model and several conventional factors that are known to affect clinical outcomes. We believe that this adjustment could more reveal the association of LDL-C with adverse

outcome. Finally, in advanced CKD, lipoproteins may be more harmful to vascular health. Unfortunately, these were not measured in our study. Future studies should evaluate the roles of other lipids and lipoproteins in the setting of severe kidney failure.

In conclusion, this study showed a significant and graded association of LDL-C level with the risk of eMACEs in Korean CKD patients. The predictive performance of LDL-C was more pronounced in patients with preserved kidney function. There was no relationship between LDL-C and risk of all-cause death, but kidney outcomes were worse in patients with high LDL-C levels. Our findings highlight the importance of lipid management in patients with CKD without kidney replacement therapy to improve clinical outcomes. However, the optimal target level of LDL-C should be addressed in future RCTs.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.numecd.2021.09.037.

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