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Association between Low-Density Lipoprotein Cholesterol Level and Cardiovascular Outcomes in Korean Adults: A Nationwide Cohort Study

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Background: To validate the treatment target of low-density lipoprotein cholesterol (LDL-C) level according to the cardiovascular disease (CVD) risk which was recommended by Korean dyslipidemia guideline.
Methods: We used the Korean National Health Insurance Service database which included 3,958,048 people aged 20 to 89 years who underwent regular health screening. The primary outcome was incident CVD, defined as a composite of myocardial infarction and stroke during the follow-up period from 2009 to 2018.
Results: The risk of CVD increased from LDL-C level of 70 mg/dL in very high-risk and high-risk groups and from 130 mg/dL in moderate-risk and low-risk groups. Adjusted hazard ratios (HRs) of LDL-C ranges 70–99, 100–129, 130–159, 160–189, and ≥190 mg/dL were 1.20 (95% confidence interval [CI], 1.08–1.33), 1.27 (1.15–1.42), 1.39 (1.23–1.56), 1.69 (1.45–1.96), and 1.84 (1.49–2.27) in very high-risk group, and 1.07 (1.02–1.13), 1.16 (1.10–1.21), 1.29 (1.22–1.36), 1.45 (1.36–1.55), and 1.73 (1.58–1.90) in high-risk group. Adjusted HRs (95% CI) of LDL-C ranges 130–159, 160–189, and ≥190 mg/dL were 1.15 (1.11–1.20), 1.28 (1.22–1.34), and 1.45 (1.36–1.54) in moderate-risk group and 1.07 (1.02–1.13), 1.20 (1.13–1.26), and 1.47 (1.37–1.57) in low-risk group.
Conclusion: We confirmed the incidence of CVD was increased in higher LDL-C range. The risk of CVD increased from ≥70 mg/dL of LDL-C in very high-risk and high-risk groups, and from ≥130 mg/dL of LDL-C in moderate-risk and low-risk groups in Korean adults.

Keywords: Cardiovascular diseases; Cholesterol; LDL; Korea

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INTRODUCTION

The prevalence of hypercholesterolemia in adults aged 20 years or older in South Korea was 20.7% in 2018, more than double compared 10 years ago [1]. It is well established that an elevated low-density lipoprotein cholesterol (LDL-C) level is one of the most important risk factors for cardiovascular disease (CVD) [2]. Lowering LDL-C has shown a close correlation with CVD risk reduction and has been used as the primary target for the prevention of CVD in many randomized controlled trials (RCTs) of statins.

Korean guidelines for dyslipidemia management including Korean Diabetes Association guidelines [3] and the Korean Society of Lipid and Atherosclerosis (KSoLA) guidelines for the management of dyslipidemia [4] also use LDL-C as the primary target for dyslipidemia management and suggest differentiating target levels of LDL-C according to CVD risk based on the results of global trials for primary and secondary prevention of CVD and expert opinions [5-10]. However, most of the RCTs presented as references in those guidelines were conducted with Caucasians. Asia showed distinctive epidemiologic characteristics of CVD from Western countries that might be due to ethnic, geographic, and economic diversities [11]. Some trials conducted with Japanese have shown different thresholds of LDL-C for the prevention of CVD [12,13] which suggest that different targets of LDL-C might be needed according to ethnicity. For that reason, evidence for lipid goals and statin therapy with the Korean population is essential to proper guidelines for the management of dyslipidemia aimed at Korean. Unfortunately, well-organized RCTs or population-based epidemiology studies that proved the effects of lowering LDL-C on the prevention of CVD in Koreans are limited. In particular, evidence of LDL-C targets for Korean people with moderate- or low-CVD risk is very scarce so far. We investigated the relationship between LDL-C levels and the development of CVD and identified the LDL-C level at which the risk of CVD increases in Korean adults according to their CVD risk using big data from the Korean National Health Insurance Service (NHIS).

METHODS

Data sources

This study used the NHIS database of claims and biennial data the of National Health Screening Program (NHSP) in the Republic of Korea recorded from January 1, 2009, to December 31, 2018. This nationwide data includes each patient's encrypted identification number, age, gender, primary diagnosis, secondary diagnoses, date of hospital visits, prescriptions received during inpatient and outpatient visits, hospital admissions, and medical and surgical procedures [14]. Prescription information includes the brand name, generic name, prescription date and duration, and route of administration. The diagnoses were coded according to the International Classification of Disease, Tenth Revision (ICD-10). The database of NHSP also included body measurements, laboratory results, and additional information on family history, lifestyle, and behavior such as family history of CVD, smoking, alcohol drinking, and regular exercise from self-reported questionnaires. This study was approved by the Institutional Review Board of Inje University Ilsan Paik Hospital (IRB No. 2019-06-026). An informed consent exemption was granted by the board. All methods were performed in accordance with the relevant guidelines and regulations.

Study subjects

Adults aged 20 years and older who underwent routine health check-ups provided by the NHIS in 2009 were selected for the analysis (n=4,234,341). After the exclusion of individuals under the age of 20 or over the age of 90 (n=1,848), those with insufficient data at least one variable (n=171,737), those with triglyceride (TG) ≥400 mg/dL (n=88,329), and those with LDL-C ≥400 mg/dL (n=14,379), 3,958,048 subjects were ultimately included.

Subjects were classified as CVD-risk categories as very high, high, moderate, and low-risk using the 2018 KSoLA guidelines [4]. Very high-risk was defined as having coronary artery disease, atherosclerotic stroke, transient ischemic attack, or peripheral artery disease. Subjects with abdominal aortic aneurysm, or diabetes were classified as a high-risk group. Subjects with two or more major cardiovascular (CV) risk factors including age (men ≥45 years, women ≥55 years), family history of premature atherosclerotic cardiovascular disease (ASCVD), hypertension, smoking, and low high-density lipoprotein cholesterol (HDL-C) level were classified as a moderate-risk group. Low-risk was defined as having one or fewer major CV risk factor. CVD risk was assessed based on the latest available measurements in the year prior to the baseline date.

Definitions of measurements

Covariates were based on the data from the index year and included age, sex, body mass index (BMI; kg/m^2), current smoking status, alcohol consumption, regular exercise, and systolic/

diastolic blood pressure. Blood samples for the measurement of serum glucose, creatinine, total cholesterol, HDL-C, and TG levels were drawn after an overnight fast. LDL-C levels were calculated from the Friedewald formula: LDL-C=total cholesterol−HDL-C−(TG/5). Non-HDL-C was calculated by subtracting HDL-C from total cholesterol. Regular exercise was defined as performing more than 30 minutes of moderate physical activity at least five times per week or more than 20 minutes of strenuous physical activity at least three times per week. Alcohol drinking habits were classified into three groups: non-drinkers, mild drinkers (daily alcohol intake <30 g/day), and heavy drinkers (daily alcohol intake ≥30 g/day).

Established CVDs were defined as the presence of at least one service claim with codes I20–25 and I63–64 during admission or at outpatient clinics, respectively [15,16]. Hypertension was defined as a blood pressure ≥140/90 mm Hg or use of an antihypertensive medication under ICD-10 codes I10–13 and I15. Type 2 diabetes mellitus (T2DM) was defined as at least one service claim with a diagnosis of T2DM based on ICD-10 codes E11–14 in the outpatient or inpatient setting and were prescribed at least one antidiabetic drug at any time over 1 year to exclude prediabetic or non-diabetic individuals. Myocardial infarction (MI) was defined as hospitalization and percutaneous coronary intervention/coronary artery bypass grafting with ICD-10 codes of I21–22. Ischemic stroke was defined as the recording of ICD-10 codes I63–64 with claims for brain magnetic resonance imaging or brain computed tomography during hospitalization.

Study outcomes

The primary outcome was a composite of newly diagnosed MI and ischemic stroke during the follow-up period from 2009 to 2018. Secondary outcomes were the incidence of MI and ischemic stroke according to the LDL-C levels in each CVD risk categories.

Statistical analysis

Baseline characteristics are presented as the mean±standard deviation or number (%). To compare subjects' clinical characteristics according to the primary outcome, the Mood median test or analysis of variance for continuous variables and the chi-square test for categorical variables were used. Incidence rate of primary outcomes was calculated by dividing the number of incident cases by the total follow-up duration (person-years). Participants were divided into the following categories according to LDL-C range: <70, 70–99, 100–129, 130–159, 160–189, and ≥190 mg/dL and non-HDL-C range: <100, 100–129, 130–159, 160–189, 190–219, and ≥220 mg/dL. Cox regression analyses were performed to estimate the risk of CVD for each LDL-C group using the <70 mg/dL group and for each non-HDL-C group using the <100 mg/dL group as the reference groups. A multivariable Cox proportional hazards model was applied that was adjusted for age, sex, BMI (kg/m^2), current smoking status, alcohol consumption, regular exercise (no, yes), hypertension (no, yes), estimated glomerular filtration rate (eGFR), family history of CVD, statin use, and TG-lowering medication. The hazard ratio (HR) and 95% confidence interval (CI) for primary outcomes were calculate by multivariable Cox proportional hazards regression analysis. All data were analyzed using SAS version 9.3 (SAS Institute Inc., Cary, NC, USA) and a $P<0.05$ was considered to indicate significance.

RESULTS

Baseline characteristics

Overall, 3,958,048 subjects were enrolled from the NHIS. The basal characteristics of participant according to risk category are shown in Table 1. The mean total follow-up duration was 9.1±1.3 years. In the cohort of 3,958,048 participants, 2,769,133 (70.0%) were in low-risk, 929,507 (23.5%) were in moderate-risk, 224,673 (5.7%) were in high-risk, and 34,735 (0.9%) were in very high-risk group. There were 3,602,282 statin non-users (90.9%) and 355,766 statin users (9.1%) at baseline. Subjects in the higher risk group were more likely to have higher fasting glucose level, older age, hypertension, and lower eGFR and to receive statins (Table 1). *P* values for the trend were <0.0001 for all variables because of the large size of the study population.

Risk of MI and stroke according to the CVD risk group

A higher incidence of MI and stroke was observed in the higher risk of CVD categories. The annual incidence of CVD defined as a composite of MI and stroke was 1.34, 5.46, 10.39, and 14.06 per 1,000 person in low-risk, moderate-risk, high-risk, and very high-risk groups, respectively. Trend tests for CVD risk categories in log-rank and Cox regression analyses for MI and stroke were all ≤0.001.

Risk of MI and stroke according to LDL-C categories

LDL-C level and CVD in the very high-risk category

There were 1,018 cases of MI and 2,948 cases of stroke in

Table 1. Baseline characteristics of subjects according to the CVD risk categories

Risk category	Low	Moderate	High	Very high
Number	2,769,133 (70.0)	929,507 (23.5)	224,673 (5.7)	34,735 (0.9)
Age, yr	43.1±12.9	55.2±12.6	60.1±10.8	63.5±11.6
Male sex	1,324,724 (47.8)	683,550 (73.5)	127,697 (56.8)	20,798 (59.9)
DM	0	0	207,171 (92.2)	9,655 (27.8)
Hypertension	317,264 (11.5)	564,227 (60.7)	145,792 (64.9)	25,398 (73.1)
Current smoker	531,760 (19.2)	434,849 (46.8)	47,648 (21.2)	6,066 (17.5)
Alcohol drinking	1,333,873 (48.2)	479,086 (51.5)	80,526 (35.8)	9,537 (27.5)
Regular exercise	479,503 (17.3)	180,788 (19.5)	53,521 (23.8)	6,832 (19.7)
Family history of CVD	132,856 (4.8)	169,517 (18.2)	18,940 (8.4)	4,490 (12.9)
Use of statin	138,309 (5.0)	122,490 (13.2)	79,834 (35.5)	15,133 (43.6)
BMI, kg/m^2	23.2±3.2	24.6±3.1	24.9±3.3	24.3±3.3
SBP, mm Hg	119.3±13.4	129.6±16.1	128.5±15.7	127.7±16.4
DBP, mm Hg	74.6±9.3	80.6±10.8	78.1±10.0	78.0±10.5
Total cholesterol, mg/dL	194.5±36.1	195.6±36.9	190.0±39.9	184.3±40.8
LDL-C, mg/dL	113.0±32.7	117.9±34.4	108.6±36.2	105.7±36. 9
HDL-C, mg/dL	59.7±28.5	46.3±14.4	52.3±29.2	52.6±32.7
Triglyceride, mg/dL	96±44.5	144±50.5	134±57.0	122±51.2
Glucose, mg/dL	93.0±15.8	98.4±20.4	138.2±50.5	107.1±35.1
eGFR, mL/min/1.73 m^2	89.5±27.4	82.3±28.9	76.3±28.7	67.9±27.3

Values are presented as number (%) or mean±standard deviation. *P* values for the trend were <0.0001 for all variables because of the large size of the study population.
CVD, cardiovascular disease; DM, diabetes mellitus; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate.

34,735 subjects of the very high-risk category. The incidence rates of MI in the very high-risk group were 3.91, 3.88, 2.98, 3.16, 4.41, and 4.52 per 1,000 person-year and the incidence rates of stroke were 8.79, 10.27, 10.63, 11.33, 12.86, and 14.29 per 1,000 person-year in each LDL-C range (<70, 70–99, 100–129, 130–159, 160–189, and ≥190 mg/dL), respectively.

Using LDL-C level <70 mg/dL as the reference, an LDL-C level ≥70 mg/dL was associated with a significant increase of CVD defined as composite of MI and stroke: adjusted HRs (aHRs) of LDL-C ranges 70–99, 100–129, 130–159, 160–189, and ≥190 mg/dL were 1.20 (95% CI, 1.08 to 1.33), 1.27 (95% CI, 1.15 to 1.42), 1.39 (95% CI, 1.23 to 1.56), 1.69 (95% CI, 1.45 to 1.96), and 1.84 (95% CI, 1.49 to 2.27), respectively (Table 2, Fig. 1). The LDL-C categories 70–99 mg/dL (HR, 1.22; 95% CI, 1.01 to 1.46), 100–129 mg/dL (HR, 1.18; 95% CI, 0.97 to 1.44), 130–159 mg/dL (HR, 1.38; 95% CI, 1.10 to 1.74), 160–189 mg/dL (HR, 1.84; 95% CI, 1.39 to 2.44), and ≥190 mg/dL (HR, 1.99; 95% CI, 1.32 to 2.99) have significant associations with risk of MI. The stroke risk also significantly increased in the LDL-C ranges 70–99 mg/dL (HR, 1.20; 95% CI, 1.06 to 1.35), 100–129 mg/dL (HR, 1.30; 95% CI, 1.15 to 1.48), 130–159 mg/dL (HR, 1.41; 95% CI, 1.23 to 1.61), 160–189 mg/dL (HR, 1.60; 95% CI, 1.34 to 1.90), and ≥190 mg/dL (HR, 1.79; 95% CI, 1.40 to 2.27) (Table 2).

However, using LDL-C level <55 mg/dL as the reference, there is no significant difference in CVD risk between LDL-C 55–69 mg/dL and LDL-C 70–99 mg/dL (Supplementary Table 1). It is probably because the incidence of CVD was low during follow-up period in very high-risk group.

LDL-C level and CVD in high-risk category

There were 6,982 cases of MI and 13,982 cases of stroke in 224,673 subjects of high-risk category. The incidence of MI in high-risk group was 3.06, 3.28, 3.47, 3.82, 4.68, and 5.82 per 1,000 person-year in the LDL-C ranges <70, 70–99, 100–129, 130–159, 160–189, and ≥190 mg/dL, respectively. The inci-

Table 2. Risk of myocardial infarction and stroke according to LDL-C categories

LDL-C, mg/dL	MI			Stroke			Composite of MI and stroke		
	No. of events	Incidence rate, /1,000 person-yr	HR (95% CI)[a]	No. of events	Incidence rate, /1,000 person-yr	HR (95% CI)[a]	No. of events	Incidence rate, /1,000 person-yr	HR (95% CI)[a]
Very high-risk group									
<70	179	3.91	1 (Reference)	395	8.79	1 (Reference)	558	12.61	1 (Reference)
70–99	339	3.88	1.22 (1.01–1.46)	876	10.27	1.20 (1.06–1.35)	1,183	14.06	1.20 (1.08–1.33)
100–129	247	2.98	1.18 (0.97–1.44)	857	10.63	1.30 (1.15–1.48)	1,078	13.52	1.27 (1.15–1.42)
130–159	154	3.16	1.38 (1.10–1.74)	535	11.33	1.41 (1.23–1.61)	666	14.26	1.39 (1.23–1.56)
160–189	72	4.41	1.84 (1.39–2.44)	203	12.86	1.60 (1.34–1.90)	272	17.55	1.69 (1.45–1.96)
≥190	27	4.52	1.99 (1.32–2.99)	82	14.29	1.79 (1.40–2.27)	106	18.82	1.84 (1.49–2.27)
P for trend			<0.0001			<0.0001			<0.0001
High-risk group									
<70	780	3.06	1 (Reference)	1,675	6.65	1 (Reference)	2,332	9.34	1 (Reference)
70–99	1,869	3.28	1.12 (1.03–1.22)	3,841	6.84	1.04 (0.98–1.10)	5,441	9.77	1.07 (1.02–1.13)
100–129	2,164	3.47	1.25 (1.15–1.36)	4,361	7.09	1.10 (1.04–1.17)	6,222	10.23	1.16 (1.10–1.21)
130–159	1,368	3.82	1.40 (1.28–1.53)	2,759	7.82	1.23 (1.16–1.31)	3,907	11.21	1.29 (1.22–1.36)
160–189	564	4.68	1.74 (1.56–1.94)	975	8.21	1.31 (1.21–1.42)	1,445	12.36	1.45 (1.36–1.55)
≥190	237	5.82	2.16 (1.87–2.51)	371	9.26	1.51 (1.34–1.69)	574	14.60	1.73 (1.58–1.90)
P for trend			<0.0001			<0.0001			<0.0001
Moderate-risk group									
<70	947	1.69	1 (Reference)	2,177	3.91	1 (Reference)	3,007	5.42	1 (Reference)
70–99	3,099	1.58	0.99 (0.92–1.07)	6,915	3.54	0.96 (0.92–1.01)	9,664	4.98	0.97 (0.93–1.01)
100–129	5,183	1.76	1.13 (1.06–1.22)	10,534	3.59	0.99 (0.95–1.04)	15,209	5.22	1.04 (0.99–1.08)
130–159	4,340	2.18	1.39 (1.29–1.49)	7,560	3.82	1.04 (0.99–1.09)	11,505	5.86	1.16 (1.11–1.20)
160–189	1,950	2.73	1.67 (1.55–1.81)	2,914	4.10	1.09 (1.03–1.15)	4,689	6.66	1.28 (1.22–1.34)
≥190	759	3.54	2.09 (1.90–2.31)	952	4.46	1.15 (1.06–1.24)	1,640	7.78	1.45 (1.36–1.54)
P for trend			<0.0001			<0.0001			<0.0001
Low-risk group									
<70	665	0.36	1 (Reference)	1,547	0.83	1 (Reference)	2,156	1.16	1 (Reference)
70–99	2,229	0.30	0.93 (0.85–1.01)	5,161	0.70	0.92 (0.87–0.98)	7,229	0.99	0.93 (0.88–0.97)
100–129	3,668	0.40	1.04 (0.96–1.13)	8,004	0.87	0.95 (0.90–1.00)	11,406	1.24	0.98 (0.93–1.02)
130–159	2,873	0.56	1.23 (1.13–1.34)	5,740	1.13	1.01 (0.95–1.06)	8,398	1.65	1.07 (1.02–1.13)
160–189	1,368	0.83	1.57 (1.43–1.72)	2,235	1.36	1.04 (0.97–1.11)	3,512	2.15	1.20 (1.13–1.26)
≥190	631	1.33	2.25 (2.02–2.52)	791	1.67	1.13 (1.03–1.23)	1,392	2.95	1.47 (1.37–1.57)
P for trend			<0.0001			<0.0001			<0.0001

LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; HR, hazard ratio; CI, confidence interval.
[a]Adjusted for age, sex, body mass index, smoking, alcohol drinking, exercise, diabetes, hypertension, estimated glomerular filtration rate, fasting triglyceride level, and use of statins.

dence of stroke was also increased in higher LDL-C categories as 6.65, 6.84, 7.09, 7.82, 8.21, and 9.26 per 1,000 person-year in the LDL-C ranges <70, 70–99, 100–129, 130–159, 160–189, and ≥190 mg/dL, respectively.

Using LDL-C level <70 mg/dL as the reference, an LDL-C level ≥70 mg/dL was associated with a significant increase of

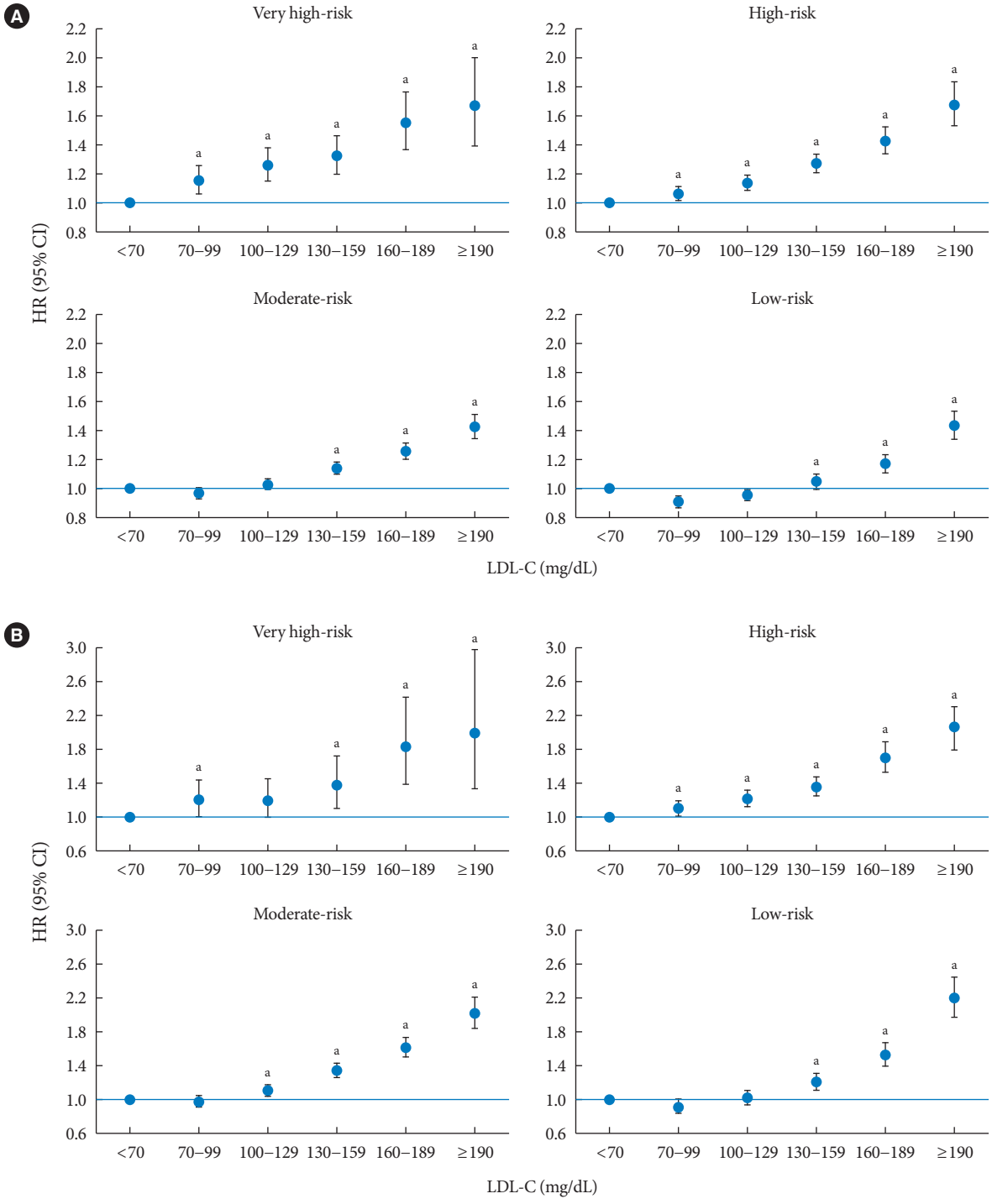

Fig. 1. Sensitivity analyses of association between the low-density lipoprotein cholesterol (LDL-C) and composite of myocardial infarction (MI) and stroke (A), MI (B), and stroke (C) stratified by cardiovascular disease risk categories; The LDL <70 mg/dL category was used as the reference for the model. Participants were divided into the following categories of LDL-C levels: <70 (reference), 70–99, 100–129, 130–159, 160–189, and ≥190 mg/dL. Hazard ratios (HRs) and 95% confidence intervals (CIs) of MI, and stroke according to the LDL-C levels. Adjusted for age, sex, body mass index, smoking, alcohol drinking, exercise, diabetes, hypertension, estimated glomerular filtration rate, fasting triglyceride level, and use of statins.

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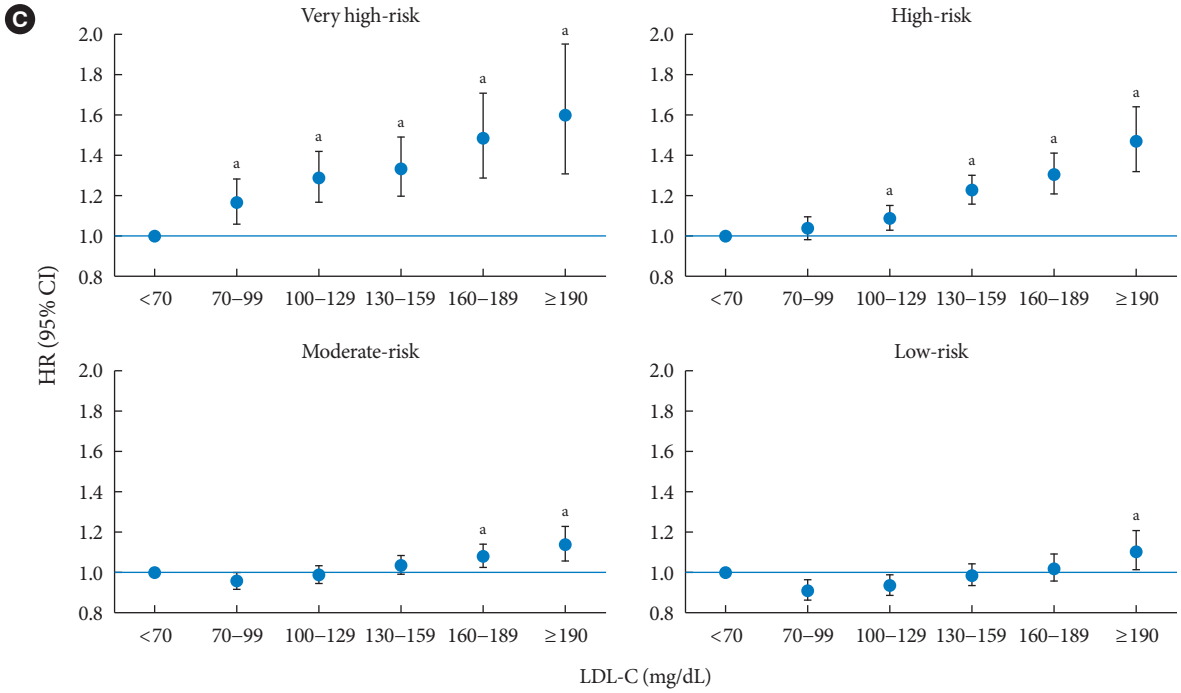

Fig. 1. Continued.

CVD: aHRs of LDL-C ranges 70–99, 100–129, 130–159, 160–189, and ≥190 mg/dL were 1.07 (95% CI, 1.02 to 1.13), 1.16 (95% CI, 1.10 to 1.21), 1.29 (95% CI, 1.22 to 1.36), 1.44 (95% CI, 1.36 to 1.55), and 1.73 (95% CI, 1.58 to 1.90), respectively. The risk of MI increased from LDL-C level 70 mg/dL, while the risk of stroke increased from ≥100 mg/dL. An LDL-C level ≥70 mg/dL was associated with a significant increase in the incidence of the composite of MI and stroke (Fig. 1). Significant associations with MI were seen for the LDL-C categories 70–99 mg/dL (HR, 1.12; 95% CI, 1.03 to 1.22), 100–129 mg/dL (HR, 1.25; 95% CI, 1.15 to 1.36), 130–159 mg/dL (HR, 1.40; 95% CI, 1.28 to 1.53), 160–189 mg/dL (HR, 1.74; 95% CI, 1.56 to 1.94), and ≥190 mg/dL (HR, 2.16; 95% CI, 1.87 to 2.51) (Table 2). Development of stroke was significantly increased in the LDL-C category 100–129 mg/dL (HR, 1.10; 95% CI, 1.04 to 1.17), 130–159 mg/dL (HR, 1.23; 95% CI, 1.16 to 1.31), 160–189 mg/dL (HR, 1.31; 95% CI, 1.21 to 1.42), and ≥190 mg/dL (HR, 1.51; 95% CI, 1.34 to 1.69) compared with the LDL-C level <70 mg/dL as the reference (Table 2).

LDL-C level and CVD in moderate-risk category

There were 16,278 cases of MI and 31,052 cases of stroke among 929,507 subjects in the moderate-risk category. The incidence of MI in moderate-risk group was 1.69, 1.58, 1.76, 2.18, 2.73, and 3.54 per 1,000 person-year in the LDL-C categories <70, 70–99, 100–129, 130–159, 160–189, and ≥190 mg/dL. The incidence of stroke was 3.91, 3.54, 3.59, 3.82, 4.10, and 4.46 per 1,000 person-year in the LDL-C ranges <70, 70–99, 100–129, 130–159, 160–189, and ≥190 mg/dL, respectively.

The composite of MI and stroke was significantly increased from LDL-C level ≥130 mg/dL: aHRs of LDL-C ranges 130–159, 160–189, and ≥190 mg/dL were 1.16 (95% CI, 1.11 to 1.20), 1.28 (95% CI, 1.22 to 1.34), and 1.45 (95% CI, 1.36 to 1.54), respectively. An LDL-C level ≥100 mg/dL was associated with a significant increase of MI risk (Fig. 1). Using LDL-C level <70 mg/dL as the reference, significant associations with MI were seen for the LDL-C ranges 100–129 mg/dL (HR, 1.13; 95% CI, 1.06 to 1.22), 130–159 mg/dL (HR, 1.39; 95% CI, 1.29 to 1.49), 160–189 mg/dL (HR, 1.67; 95% CI, 1.55 to 1.81), and ≥190 mg/dL (HR, 2.09; 95% CI, 1.90 to 2.31). An LDL-C level ≥160 mg/dL was significantly associated with an increase of stroke risk (Fig. 1). Significant associations with stoke were observed for the LDL-C ranges 160–189 mg/dL (HR, 1.09; 95% CI, 1.03 to 1.15) and ≥190 mg/dL (HR, 1.15; 95% CI, 1.06 to 1.24) compared with LDL-C level <70 category (Table 2).

LDL-C level and CVD in low-risk group

There were 11,434 cases of MI and 23,478 cases of stroke in

Table 3. Risk of myocardial infarction and stroke according to non-HDL-C categories

Non-HDL-C, mg/dL	MI			Stroke			MI or stroke		
	No. of events	Incidence rate, /1,000 person-yr	HR (95% CI)[a]	No. of events	Incidence rate, /1,000 person-yr	HR (95% CI)[a]	No. of events	Incidence rate, /1,000 person-yr	HR (95% CI)[a]
Very high-risk group									
<100	217	3.80	1 (Reference)	492	8.78	1 (Reference)	691	12.51	1 (Reference)
100–129	292	3.51	1.12 (0.94–1.34)	844	10.41	1.22 (1.09–1.37)	1,106	13.82	1.20 (1.09–1.32)
130–159	248	3.22	1.25 (1.03–1.51)	771	10.32	1.27 (1.13–1.43)	994	13.46	1.26 (1.14–1.40)
160–189	136	3.03	1.25 (1.00–1.56)	515	11.86	1.45 (1.28–1.66)	631	14.70	1.40 (1.25–1.57)
190–219	86	5.00	1.99 (1.54–2.57)	201	11.99	1.47 (1.24–1.74)	281	17.10	1.61 (1.40–1.86)
≥220	38	5.54	2.16 (1.52–3.06)	107	16.41	1.98 (1.60–2.45)	141	22.12	2.05 (1.71–2.47)
P for trend			<0.0001			<0.0001			<0.0001
High-risk group									
<100	848	2.94	1 (Reference)	1,869	6.56	1 (Reference)	2,590	9.17	1 (Reference)
100–129	1,639	3.02	1.10 (1.01–1.19)	3,550	6.62	1.05 (0.99–1.11)	4,951	9.36	1.07 (1.02–1.12)
130–159	2,100	3.60	1.37 (1.26–1.49)	4,135	7.20	1.16 (1.10–1.23)	5,931	10.44	1.23 (1.17–1.29)
160–189	1,368	3.84	1.50 (1.37–1.64)	2,690	7.67	1.27 (1.20–1.35)	3,849	11.11	1.35 (1.28–1.42)
190–219	671	4.95	1.92 (1.73–2.13)	1,166	8.73	1.45 (1.35–1.56)	1,732	13.18	1.60 (1.51–1.70)
≥220	325	5.92	2.34 (2.06–2.66)	512	9.48	1.63 (1.47–1.79)	785	14.82	1.85 (1.71–2.01)
P for trend			<0.0001			<0.0001			<0.0001
Moderate-risk group									
<100	1,023	1.73	1 (Reference)	2,394	4.07	1 (Reference)	3,296	5.63	1 (Reference)
100–129	2,950	1.56	1.00 (0.93–1.08)	6,902	3.67	1.02 (0.97–1.07)	9,501	5.07	1.01 (0.97–1.05)
130–159	4,791	1.72	1.17 (1.09–1.25)	9,928	3.58	1.05 (1.01–1.10)	14,255	5.17	1.09 (1.05–1.14)
160–189	4,295	2.13	1.47 (1.37–1.58)	7,360	3.66	1.11 (1.06–1.16)	11,266	5.65	1.22 (1.18–1.27)
190–219	2,193	2.71	1.82 (1.69–1.96)	3,214	3.99	1.19 (1.13–1.26)	5,205	6.52	1.39 (1.33–1.45)
≥220	1,012	3.55	2.32 (2.12–2.53)	1,219	4.29	1.26 (1.18–1.35)	2,144	7.64	1.60 (1.51–1.69)
P for trend			<0.0001			<0.0001			<0.0001
Low-risk group									
<100	1,017	0.27	1 (Reference)	2,429	0.63	1 (Reference)	3,357	0.88	1 (Reference)
100–129	2,449	0.31	0.99 (0.92–1.07)	5,787	0.73	0.97 (0.92–1.01)	8,070	1.022	0.98 (0.94–1.02)
130–159	3,330	0.43	1.16 (1.08–1.24)	7,362	0.96	1.04 (0.99–1.09)	10,451	1.36	1.08 (1.04–1.12)
160–189	2,579	0.62	1.45 (1.35–1.57)	4,852	1.17	1.10 (1.05–1.16)	7,245	1.75	1.21 (1.16–1.26)
190–219	1,289	0.89	1.86 (1.71–2.03)	2,023	1.39	1.18 (1.11–1.25)	3,224	2.23	1.38 (1.32,1.45)
≥220	674	1.39	2.67 (2.42–2.95)	821	1.69	1.30 (1.20–1.41)	1,458	3.02	1.71 (1.61–1.82)
P for trend			<0.0001			<0.0001			<0.0001

HDL-C, high-density lipoprotein cholesterol; MI, myocardial infarction; HR, hazard ratio; CI, confidence interval.
[a]Adjusted for age, sex, body mass index, smoking, alcohol drinking, exercise, diabetes, hypertension, estimated glomerular filtration rate, fasting triglyceride level, and use of statins.

2,769,133 subjects of low-risk category. The incidence of MI in subjects with low-risk of CVD was 0.36, 0.30, 0.40, 0.56, 0.83, and 1.33 per 1,000 person-year in each LDL-C ranges <70, 70–99, 100–129, 130–159, 160–189, and ≥190 mg/dL. In case of stroke, the incidence was 0.83, 0.70, 0.87, 1.13, 1.36, and 1.67 per 1,000 person-year in the LDL-C ranges <70, 70–99, 100–

129, 130–159, 160–189, and ≥190 mg/dL, respectively.

In low-risk of CVD group, an LDL-C level ≥130 and ≥190 mg/dL was associated with a significant increase of MI and stroke risk, respectively (Fig. 1). The composite of MI and stroke was significantly increased from LDL-C level ≥130 mg/dL: aHRs of LDL-C ranges 130–159, 160–189, and ≥190 mg/dL were 1.07 (95% CI, 1.02 to 1.13), 1.20 (95% CI, 1.13 to 1.26), and 1.47 (95% CI, 1.37 to 1.57), respectively. The significant associations with MI were seen for the LDL-C categories 130–159 mg/dL (HR, 1.23; 95% CI, 1.13 to 1.34), 160–189 mg/dL (HR, 1.57; 95% CI, 1.43 to 1.72), and ≥190 mg/dL (HR, 2.25; 95% CI, 2.02 to 2.52) (Table 2). The risk of stroke was increased only in the LDL-C category ≥190 mg/dL (HR, 1.13; 95% CI, 1.03 to 1.23) when the LDL-C level <70 mg/dL was used as the reference.

Risk of MI and stroke according to non-HDL categories

Non-HDL-C concentrations in blood were strongly associated with risk of CVD in all risk categories (Table 3). The composite of MI and stroke was significantly increased from non-HDL-C level ≥100 mg/dL in very high-risk (aHR, 1.2; 95% CI, 1.09 to 1.32) and high-risk (aHR, 1.07; 95% CI, 1.02 to 1.12) groups, and from non-HDL-C level ≥130 mg/dL in the moderate-risk (aHR, 1.09; 95% CI, 1.05 to 1.14) and low-risk (aHR, 1.08; 95% CI, 1.04 to 1.12) groups when using non-HDL-C level <100 mg/dL as the reference.

DISCUSSION

In this study which is a population-based observational study of Korean population, the incidence of the composite of MI and stoke increased when LDL-C levels were higher. We confirmed that the risk of MI and stroke increased at ≥70 mg/dL in very high-risk and high-risk groups, and ≥130 mg/dL of LDL-C level in moderate-risk, and low-risk of CVD categories. There have been studies on relationship of CV risk and LDL-C level in very high-risk or high-risk groups such as patients with CVD, chronic kidney disease or diabetes in Korean population [16-18]. However, this is the first study that identified the LDL-C level from which CVD risk increased in moderate and low CVD-risk categories in Korean.

Most guidelines for management of dyslipidemia suggest 'treat to target' goals for LDL-C levels according to CVD-risk categories. The guidelines of American College of Cardiology (ACC)/American Heart Association (AHA) on the management of dyslipidemia published in 2013 emphasized the potency of statin instead of 'treat to target' goals for LDL-C levels [19]. However, the updated 2018 ACC/AHA guideline suggested an LDL-C threshold of 70 mg/dL to consider addition of non-statins to statin therapy for very-high risk category of CVD [20]. The latest guideline of 2019 European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) recommended that an LDL-C goal of <1.4 mmol/L (55 mg/dL) or at least 50% reduction of the baseline LDL-C level should be achieved in very high-risk patients [21]. The KSoLA guidelines for dyslipidemia which is representative guidelines of Korea published in 2018 also recommended differentiating targets of LDL-C concentration based on the level of CVD risk categories [4]. The LDL-C goal suggested by KSoLA as <70 mg/dL in a very high-risk group are based on the results of global RCTs, meta-analyses and observational studies that mostly enrolled Caucasians [4]. In a randomized study of statins in 10,001 patients with stable angina, 22% relative reduction in risk in the high-intensity statin group in which LDL-C level was near 70 mg/dL compared to the moderate-intensity statin group [22]. In the meta-analyses of individual participant data from statin RCTs, 29% significant further reductions in risk (99% CI, 2 to 48; P=0·007) in those who had LDL-C lower than 76 mg/dL (mean 65 mg/dL) [5].

Unfortunately, there is scarce evidence conducted with Korean population. The present study included almost all Korean adult population, showed that CVD risk was increased from 70 mg/dL of LDL-C level in very high-risk group. This result supports that a recommended <70 mg/dL LDL-C level in very high-risk group for CVD prevention is proper for Korean. In a RCT of patients with ischemic stroke conducted in France and South Korea, patients who had a target LDL-C level of <70 mg/dL had a lower risk of subsequent CV events than those who had a target range of 90 to 110 mg/dL [23]. However, in subgroup analysis, there was a lack of power to detect a significant effect in Korean patients. The difference between two countries might be caused by the gap of follow-up durations which was 2.0 years among Korean patients as compared with 5.3 years among the French patients.

Current Korean guidelines recommend LDL-C goal as <100 mg/dL for high-risk group including patients with diabetes, while recommend more strict control of LDL-C to <70 mg/dL if patients with diabetes have target organ damage or major risk factors of CVD such as family history of premature CVD, smoking and hypertension [3,4]. In this study, the risks of MI and stroke were both increased from 70 mg/dL of LDL-C level

in high-risk group. Among the high-risk group in our study defined as subjects with abdominal aortic aneurysm, or diabetes, 92% were consisted of patients with diabetes. These findings suggest that lower goal of LDL-C level compared to current guidelines may be appropriate for Korean patients with diabetes although we did not analyze according to the presence of combined major CV risk factors or target organ damages. The study using NHIS data also showed similar results that the risk of CVD was significantly higher in those taking statins with an LDL-C level ≥70 mg/dL in Koreans with T2DM without pre-existing CVD [17]. The study of LDL-C target for patients with diabetes according to existence of target organ damage or major risk factors of CVD will be needed.

For moderate-risk group which was defined as two or more major risk factors other than LDL-C such as smoking, hypertension, age, family history of premature ASCVD and low HDL-C level, the goal level of LDL-C was recommended as <130 mg/dL from the 2018 KSoLA guideline [4]. In our study, the risk of MI and stroke increased at ≥130 mg/dL of LDL-C level in moderate-risk of CVD category which supports that the KSoLA recommendation of LDL-C target for moderate-risk group is proper in Korean population.

For low-risk group defined as one or fewer major risk factor other than LDL-C, the 2018 KSoLA guidelines recommended to consider interventions when LDL-C is above 160 mg/dL [4]. However, subsequent studies show supporting results that CVD risk assessment is underestimated in low-risk group especially in young adults. In young adults, the risks that can arise from long-term accompanying risk factors are overlooked [24]. In Justification for the Use of Statin in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) trial with healthy adult men and women with a C-reactive protein ≥2 mg/L and LDL-C levels below 130 mg/dL, rosuvastatin therapy reduced the primary end point of first major CV events and all-cause mortality (HR, 0.56 and 0.80, respectively) [25]. The final LDL-C in JUPITER trial was 55 mg/dL in the statin group. In the Heart Outcomes Prevention Evaluation-3 (HOPE-3) trial which included patients with at least one CVD risk factor and 128 mg/dL of the mean baseline LDL-C level, also revealed the reduction in the development of CVD with statin therapy. Interestingly significant CVD benefit was also showed in subgroup of the baseline LDL-C level <112.3 mg/dL [26]. According to these data, the ESC/EAS guidelines was updated to lower target to treat for low-risk group. Low-risk group classified as the calculated Systematic Coronary Risk Estimation (SCORE) <1% for 10-year risk of fatal CVD was recommended to intervene when LDL-C was above 190 mg/dL in the 2016 guidelines [27]. However, this was updated to intervene when LDL-C was above 115 mg/dL in the 2019 guidelines. Our study showed an increase in the risk of MI and stroke from LDL-C 130 mg/dL and from non-HDL-C 130 mg/dL in the low-risk group, suggesting the possibility that the target of LDL-C should be more strictly modified for the low-risk group in the Korean guideline.

The LDL-C levels at which the risk increases were lower for MI than stroke in high-risk (70 mg/dL vs. 100 mg/dL), moderate-risk (100 mg/dL vs. 160 mg/dL), and low-risk (130 mg/dL vs. 190 mg/dL) groups. Hypertension preferentially associated with incidence of stroke, whereas hypercholesterolemia was more strongly associated with the development of coronary heart disease in several studies. In the EPIC-Norfolk population study, LDL-C was strongly associated with CVD (aHR highest vs. lowest quartile 1.63; 95% CI, 1.44 to 1.86), but not with ischemic stroke (aHR highest vs. lowest quartile 1.28; 95% CI, 0.88 to 1.86) [28]. In the multi-ethnic Women's Health Initiative Observational Study, multivariable aHRs in non-HDL-C were 1.16 (95% CI, 1.06 to 1.28) for coronary artery disease, 0.97 (95% CI, 0.88 to 1.07) for ischemic stroke, and 0.76 (95% CI, 0.63 to 0.91) for hemorrhagic stroke [29]. These data support that the heterogeneous impact of risk factors on different arterial diseases might be the cause of difference of LDL-C levels at which the risk of MI and stroke increases in this study.

This study has several limitations. First, ICD-10 classification used for diagnosis of dyslipidemia, pre-existing CVDs and risk factors can be not accurate in some cases. In particular, individuals with significant carotid artery stenosis who were classified to high-risk group, were not included. Also, to make up for the reliability of diagnosis with ICD-10, we defined MI and stroke by ICD-10 codes with more than 3 days of hospitalization to exclude the patients who were hospitalized for follow-up examination of coronary angiography. Second, age, sex, BMI, smoking, alcohol consumption, regular exercise, use of statins, and hypertension was adjusted but other variables that may affect the development of CVDs such as socioeconomic status, diet, kidney diseases, and conditions specific to women (e.g., preeclamsia, remature menopause), or inflammatory diseases were not included in the analysis. Third, the management status of CVD risk factors such as diabetes, hypertension as well as statin therapy was not considered in this study. In addition, we were unable to obtain clinical informa-

tion on glycosylated hemoglobin levels, high sensitivity C-reactive protein [30], and medications that an affect the development of CVD. Fourth, the level of LDL-C at which the risk of CVD increases could be different according to use of lipid-lowering agents. However, the use of lipid-lowering agents could not be considered in this study because subjects could be treated with lipid-lowering agents during the follow-up period. Fifth, the cohort in this study is comprised only of residents of South Korea so the results may not fully generalize to other populations. Lastly, our study was limited in that time-varying Cox regression was not performed. Despite these limitations, this study has strength that reflect real-world longitudinal data of nationwide Korean adult population.

In summary, the present study shows that the incidence of composite of MI and stroke increased at ≥70, ≥70, ≥130, and ≥130 mg/dL of LDL-C level in very high-risk, high-risk, moderate-risk, and low-risk of CVD categories respectively. To the best our knowledge, this is the first study that assessed the LDL-C level from which CVD risk increased in moderate and low CVD-risk categories in Korean.

SUPPLEMENTARY MATERIALS

Supplementary materials related to this article can be found online at https://doi.org/10.4093/dmj.2021.0320.

CONFLICTS OF INTEREST

Junghyun Noh was associate editors of the *Diabetes & Metabolism Journal* from 2020 to 2021. Hyeon Chang Kim has been statistical advisor of the *Diabetes & Metabolism Journal* since 2021. In-Kyung Jeong was editor in chief of the *Diabetes & Metabolism Journal* from 2020 to 2021. They were not involved in the review process of this article. Otherwise, there was no conflict of interest.

AUTHOR CONTRIBUTIONS

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Acquisition, analysis, or interpretation of data: J.N., M.K.M., E.J.R., S.H.P., H.C.K., B.J.L., H.J.K., S.C., J.O.N., Y.Y.H., B.J.K., K.D.H., I.K.J.
Drafting the work or revising: J.N., I.K.J.
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