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Statin therapy in individuals with intermediate cardiovascular risk

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ABSTRACT

Background: As intermediate cardiovascular risk group accounts for a large part of the total population, determining appropriate cholesterol target in this population is critical. Herein, we investigated the optimal low-density lipoprotein cholesterol (LDL-C) level in individuals with intermediate cardiovascular risk after statin therapy.

Methods: This was a nationwide observational and validation cohort study (median duration of follow-up: 7.5 and 8.7 years, respectively), using data from the Korean National Health Insurance Service and a tertiary hospital database. Among individuals who underwent regular health examinations, those with ≥2 cardiovascular risk factors except diabetes mellitus, LDL-C 100–189 mg/dL, and newly used statins were enrolled. Of the 358,694 screened people, 57,594 met the inclusion criteria, of whom 27,793 were finally analyzed. The study population was stratified according to post-treatment LDL-C levels as follows: <100, 100–119, 120–139, and ≥ 140 mg/dL. The primary outcome variable was composite cardiovascular events (myocardial infarction, coronary revascularization, and ischemic stroke). From the patients screened of Severance Hospital cohort, 1859 meeting inclusion criteria were used for validation.

Results: The rates of composite events ranged from 7.74 to 9.10 (mean 8.38)/1000 person-years in the three lower LDL-C groups. Adjusted hazard ratios (aHRs) ranged from 0.78 to 0.95 in the three groups with lower LDL-C, and a lower event risk was more evident in the groups that achieved LDL-C levels <120 mg/dL (p = 0.001–0.009). The total mortality risk did not differ between groups. In the validation cohort, the mean rate of composite events was 10.83/1000 person-years. aHRs ranged from 0.52 to 0.78 in the groups with lower LDL-C, and a lower risk was more obvious in patients who achieved LDL-C levels <100 mg/dL (p = 0.006–0.03).

Conclusions: Individuals with intermediate cardiovascular risk who achieved LDL-C levels <120 mg/dL after statin therapy had lower event risk. This result provides clinically useful evidence on target LDL-C levels in this population.

1. Introduction

Many patients are classified as having an intermediate cardiovascular risk and experience cardiovascular events [1]. Although many individuals in this group may benefit from lipid-lowering therapy, the 'number needed to treat' can be too high for all to feasibly undergo such therapy. Additionally, performing statin therapy and lowering low-density lipoprotein cholesterol (LDL-C) to target levels in this population are critical issues for society and individuals. Therefore, guidelines for lipid-lowering therapy and determining treatment targets are important in this group [2].

Although the utility of statins for primary prevention in the

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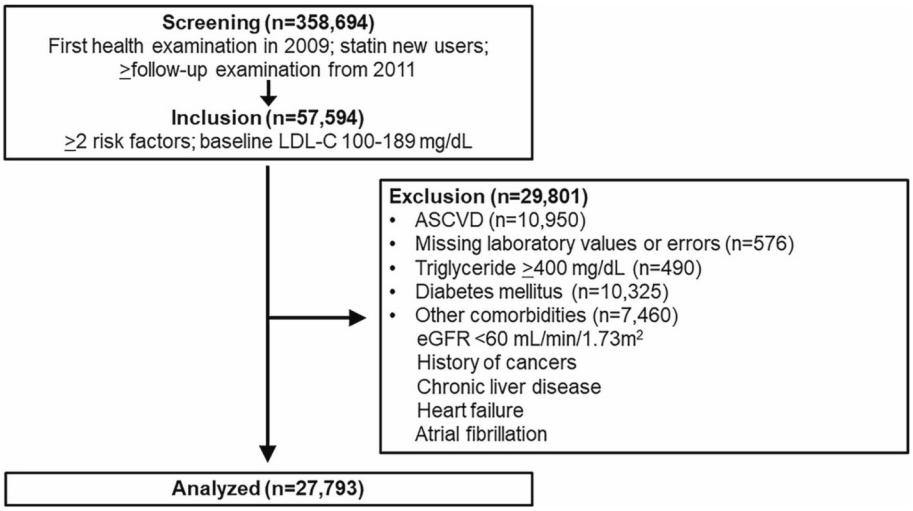

Fig. 1. Flow chart showing patient enrollment. Patients were enrolled according to the inclusion and exclusion criteria.
ASCVD: atherosclerotic cardiovascular disease; eGFR: estimated glomerular filtration rate.

intermediate-risk group has been debated [3], many patients are eligible for statin therapy according to the latest guidelines [4,5]. Meanwhile, the LDL-C target for this risk group is <100 mg/dL in the European guidelines [4], which were set based on a meta-analysis by the Cholesterol Treatment Trialist Collaborators [6]. However, this meta-analysis did not provide strong evidence to set a specific LDL-C target in this group [6]. In contrast, the American guidelines recommend prescribing moderate-intensity statins rather than aiming for specific targets in patients in this risk group with LDL-C 70–189 mg/dL [5]. If treated in this manner, post-treatment LDL-C levels may range from <50–130 mg/dL, with treatment effect dependent on baseline levels. This American recommendation was set based on previous meta-analyses [6,7] and clinical trials [8–10]. Participants in the above-mentioned trials were commonly treated with moderate-intensity statins but had diverse baseline LDL-C levels. These trials showed a wide range of post-treatment LDL-C levels, and it was difficult to determine specific levels as treatment targets based on these results alone. Unfortunately, the literature used to support treatment targets for primary prevention in major guidelines lack trials analyzing groups with different LDL-C levels.

High-quality data to support the use of lipid-lowering therapies and to suggest LDL-C targets are also limited in Asia. Although the Japanese guidelines have their own LDL-C targets for intermediate-risk populations, these are based on meta-analyses from other countries [11], the evidence of which is not sufficiently strong to support specific treatment targets. We aimed to identify the optimal LDL-C levels for managing individuals at intermediate cardiovascular risk with statin therapy.

2. Methods

The study was approved by the Institutional Review Board of Severance Hospital (4-2022-0802) and the National Health Insurance Service (NHIS) of Korea (NHIS 2023-1-031) and was conducted in accordance with the Declaration of Helsinki. As only anonymous and de-identified information extracted from the database was used for health screening, the requirement for informed consent was waived.

2.1. Data sources and study population: two cohorts

This nationwide cohort study was based on data from the NHIS of Korea [12,13] collected during the biennial health examination undertaken by Korean adults aged ≥20 years. This examination includes self-questionnaires on medical history, physical examinations, and blood tests including complete blood counts and lipid profiles [14].

The flow chart of patient enrollment is shown in Fig. 1. We initially screened all individuals who underwent the first NHIS health examination between January and December 2009 with at least one follow-up examination. Only individuals who initiated statin therapy after their first health examination were included in this study. Final follow-up was performed in December 2019. Individuals with an intermediate cardiovascular risk were enrolled. This risk category was defined by the presence of two or more of the following conditions in addition to LDL-C levels 100–189 mg/dL: 1) men ≥45 years or women ≥55 years old, 2) family history of premature coronary artery disease, 3) hypertension, 4) smoking, 5) high-density lipoprotein-cholesterol levels <40 mg/dL. Coronary artery disease diagnosed at <55 years of age in male or < 65 years of age in female was defined as premature.

The risk groups were determined by categorizing several relevant guidelines for lipid-lowering therapy as follows: 2004 American guidelines [15], 2018 American guidelines [5], and 2019 European guidelines [4]. In the current study, we selected individuals with intermediate risk, not by a 10-year risk calculation, but rather as a function of the number of risk factors. Therefore, according to the above-mentioned guidelines, our selected individuals may partly include those with higher risk scores than those in the intermediate-risk group. However, a recent study reported that the Framingham risk score, pooled cohort equation, and European SCORE all overestimated cardiovascular risk by 10 %, 41 %, and 52 %, respectively [16]. Therefore, most individuals included in our study were expected to fall within the intermediate-risk group.

The exclusion criteria were as follows: prior cardio- or cerebrovascular disease, missing laboratory values or suspicious errors on lipids, death or cardio- or cerebrovascular events in <1-year follow-up, diabetes mellitus, estimated glomerular filtration rate < 60 mL/min/1.73 m^2, and a history of cancer, chronic liver disease, heart failure, or atrial fibrillation. Individuals with triglyceride levels ≥400 mg/dL were also excluded because the LDL-C values were calculated using the Friedewald formula. Follow-up LDL-C levels were obtained 2 years after the initial health examination.

Data from a tertiary hospital cohort for validation were withdrawn from patients who visited the outpatient clinic of the Cardiology Division of Severance Hospital (Seoul, Korea) for cardiovascular examination or risk factor control. The first date of the patient's visit ranged from May 2005 to December 2021. Most inclusion and exclusion criteria for the validation cohort were the same as those mentioned above. In this cohort, patients who inconsistently used statins (<80 % of the follow-up period) were excluded.

Table 1
Clinical characteristics of the study population: the nationwide cohort.

Variable	Total (n = 27,793; 100 %)	Post-treatment LDL-C, mg/dL				p
		<100 (n = 10,324; 37.1 %)	100–119 (n = 4640; 16.7 %)	120–139 (n = 4517; 16.3 %)	≥140 (n = 8312; 29.9 %)	
Age, years	58.8 ± 10.0	58.3 ± 9.9	57.9 ± 10.0	57.5 ± 10.2	57.2 ± 10.0	<0.0001
Male	16,879 (60.8)	6307 (61.1)	2785 (60.0)	2822 (62.5)	4965 (59.7)	0.01
Medical history						
Hypertension	19,653 (70.7)	8578 (83.1)	3378 (72.8)	3012 (66.7)	4685 (56.4)	<0.0001
Current smoker	7425 (26.7)	2517 (24.4)	1236 (26.6)	1242 (27.5)	2430 (29.2)	<0.0001
HDL-C < 40 mg/dL	3478 (12.5)	1306 (12.7)	593 (12.8)	613 (13.6)	966 (11.6)	0.01
Number of risk factors						<0.0001
2	19,918 (71.7)	7044 (68.2)	3300 (71.1)	3366 (74.5)	6208 (74.7)	
3	6701 (24.1)	2749 (26.6)	1139 (24.6)	971 (21.5)	1842 (22.2)	
4	1174 (4.2)	531 (5.1)	201 (3.3)	180 (3.9)	262 (3.2)	
Body mass index, kg/m^2	25.0 ± 3.0	25.2 ± 3.1	25.1 ± 3.1	24.9 ± 3.0	24.9 ± 3.0	<0.0001
Baseline lipid profile, mg/dL						
Total cholesterol	230 ± 26	224 ± 26	228 ± 26	229 ± 25	239 ± 25	<0.0001
Triglyceride	146 (104, 206)	146 (104, 206)	145 (105, 209)	145 (102, 205)	146 (105, 205)	0.37
HDL-C	53.2 ± 21.4	53.4 ± 23.4	53.3 ± 24.0	53.5 ± 19.8	52.8 ± 17.7	0.20
LDL-C	145 ± 23	139 ± 22	143 ± 23	144 ± 22	153 ± 21	<0.0001
Post-treatment LDL-C, mg/dL	117 ± 39	77 ± 16	110 ± 6	130 ± 6	165 ± 20	<0.0001
Statin intensity						<0.0001
Higher moderate	15,723 (24.2)	2.517 (24.4)	993 (21.4)	1063 (23.5)	2150 (25.9)	
Lower moderate	20,125 (72.4)	7530 (72.9)	3436 9 (74.1)	3259 (72.2)	5900 (71.0)	
Low	945 (3.4)	277 (2.7)	211 (4.6)	195 (4.3)	262 (3.2)	
Antiplatelet agents	9016 (32.4)	4188 (40.6)	1542 (33.2)	1372 (30.4)	1914 (23.0)	<0.0001

LDL-C, low-density lipoprotein cholesterol; HDL—C, high-density lipoprotein cholesterol.

2.2. Variables and definitions

The participants' demographic variables, including age, sex, and cardiovascular risk factors were collected. Blood samples were obtained after overnight fasting, and lipid levels were assayed using an enzymatic method. Diabetes and hypertension were defined by prior diagnoses (ICD-10 codes) or use of at least one antidiabetic or antihypertensive medications, respectively. Statin intensity was defined according to the 2018 American College of Cardiology/American Heart Association guidelines [5]. The majority of the study population was prescribed moderate-intensity statins. To determine whether there was a difference in statin intensities between the groups, we divided those taking moderate-intensity statins into two groups, as previously described [17]: atorvastatin 20 mg or similar statins (higher moderate), and atorvastatin 10 mg or similar statins (lower moderate). Because the number of subjects who received high-intensity statins was too small, they were combined with those who received higher moderate-intensity statins.

The primary endpoint was a composite of myocardial infarction (MI), coronary revascularization (percutaneous coronary intervention or coronary artery bypass grafting), ischemic stroke, or transient ischemic attack (TIA). Secondary endpoints were defined as each component of the primary endpoint and total mortality. MI was defined using the ICD-10 codes during hospital admission or outpatient records. Percutaneous coronary intervention was defined by the procedural codes M655*–M657* in the NHIS, and coronary artery bypass grafts were defined by the codes OA631*–OA639*, OB631*–OB639*, OA641*, OA642*, O0161*–O0171*, and O1641*–O1647*. Ischemic stroke/TIA was defined from the presence of ICD-10 codes during hospital admission and claims for brain imaging tests. Total mortality was defined as that in the NHIS linked to the data provided by Statistics Korea [18]. The study population was followed until the date of a composite event or death.

To evaluate the outcomes according to follow-up LDL-C levels, the study population of the nationwide cohort was grouped by LDL-C levels as follows: <100, 100–119, 120–139, and ≥140 mg/dL. As post-treatment LDL-C levels in the Severance Hospital cohort were relatively low, these individuals were grouped by LDL-C levels as follows: <80, 80–99, 100–119, and ≥ 120 mg/dL.

2.3. Statistical analysis

Continuous variables were tested for normality using the Shapiro-Wilk normality test. Normally distributed variables are presented as mean ± standard deviation (SD) and non-normally distributed variables as the median (interquartile ranges). Categorical variables were presented as numbers (percentages). Analysis of variance test and chi-square test were used to compare continuous and categorical variables, respectively. Variables with non-normal distribution were compared using Kruskal–Wallis test.

Cox proportional hazards models were used to analyze the association between patient groups, the risk of composite events, and total mortality. Hazard ratios (HRs) and confidence intervals (CIs) were calculated for both unadjusted and adjusted models. Overall, nine pre-specified potential confounders were used in the adjusted model: age, sex, body mass index, hypertension, smoking, triglyceride, baseline LDL-C, and antiplatelet agents. The risk of events was compared between the reference group and patients with lower follow-up LDL-C levels. Subgroup analysis according to sex was conducted. Two-sided p value of <0.05 was considered significant.

3. Results

3.1. Baseline characteristics

Of the 358,694 people screened from a nationwide cohort, 57,594 met the inclusion criteria. After excluding ineligible individuals, 27,793 individuals (mean age: 58.8 years; males, 60.8 %) were finally analyzed (Fig. 1). The mean age, body mass index, proportion of hypertension, number of risk factors greater than three, and antiplatelet agent use were higher in the groups with lower post-treatment LDL-C levels. Conversely, the baseline total and LDL-C levels and the proportion of current smokers were lower in these groups. The participants' demographic variables, including age, sex, and cardiovascular risk factors, are presented in Table 1. We were unable to obtain detailed data on generic names and doses of statins from the nationwide cohort.

Of the 93,044 participants screened in the Severance Hospital cohort, 13,818 met the inclusion criteria. After excluding 11,959

Table 2
Composite events and total mortality according to post-treatment LDL-C levels: the nationwide cohort[a].

Variables	Follow-up LDL-C, mg/dL	Number of patients	Events	Duration, person-year	Rate (/1000 person-year)	HR (95 % CI) (Model 1)	p	HR (95 % CI) (Model 2)	p
Composite events	Total	27,793	1676	199,895	8.38				
	<100	10,324	577	74,534	7.74	0.85 (0.76, 0.96)	0.007	0.78 (0.69, 0.89)	0.001
	100–119	4640	265	33,486	7.91	0.87 (0.75, 1.01)	0.06	0.82 (0.71, 0.95)	0.009
	120–139	4517	293	32,403	9.04	0.99 (0.86, 1.15)	0.93	0.95 (0.83, 1.10)	0.51
	≥140	8312	541	59,472	9.10	1		1	
MI	Total	27,793	544	203,769	2.67				
	<100	10,324	189	75,841	2.49	0.78 (0.64, 0.96)	0.02	0.78 (0.63, 0.96)	0.02
	100–119	4640	66	34,140	1.93	0.61 (0.46, 0.80)	0.0005	0.60 (0.45, 0.80)	0.004
	120–139	4517	96	33,073	2.90	0.91 (0.72, 1.17)	0.47	0.91 (0.71, 1.16)	0.45
	≥140	8312	193	60,715	3.18	1		1	
Coronary revascularization	Total	27,793	598	202,222	2.96				
	<100	10,324	192	74,594	2.54	0.76 (0.63, 0.93)	0.007	0.71 (0.58, 0.88)	0.002
	100–119	4640	90	34,027	2.64	0.79 (0.62, 1.02)	0.07	0.76 (0.59, 0.98)	0.03
	120–139	4517	114	32,984	3.46	1.04 (0.82, 1.31)	0.75	1.00 (0.79, 1.26)	0.97
	≥140	8312	202	60,617	3.33	1		1	
Ischemic stroke/TIA	Total	27,793	827	213,644	3.87				
	<100	10,324	286	75,413	3.79	0.87 (0.74, 1.03)	0.12	0.79 (0.66, 0.94)	0.009
	100–119	4640	136	33,890	4.01	0.93 (0.75, 1.14)	0.46	0.86 (0.70, 1.06)	0.16
	120–139	4517	143	43,925	4.34	1.00 (0.82, 1.23)	0.99	0.95 (0.78, 1.17)	0.65
	≥140	8312	262	60,416	4.34	1		1	
Total mortality	Total	27,793	1053	205,397	5.13				
	<100	10,324	400	76,346	5.23	1.03 (0.89, 1.19)	0.70	0.90 (0.77, 1.06)	0.20
	100–119	4640	177	34,326	5.16	1.01 (0.84, 1.22)	0.90	0.92 (0.76, 1.11)	0.36
	120–139	4517	164	33,386	4.91	0.97 (0.80, 1.17)	0.72	0.87 (0.72, 1.05)	0.15
	≥140	8312	312	61,339	5.08	1		1	

LDL-C, low-density lipoprotein cholesterol; HR, hazard ratio; CI, confidence interval; MI, myocardial infarction; TIA, transient ischemic attack.
Model 1: unadjusted.
Model 2 was adjusted for age, sex, body mass index, hypertension, smoking, triglycerides, low-density lipoprotein cholesterol, and antiplatelet therapy.
p values are from Cox proportional hazard model.
[a] Median follow-up duration: 7.5 years.

individuals, 1859 individuals (mean age: 62.6 years; men: 50.8 %) were analyzed (Fig. S1). The proportion of male patients tended to be higher, whereas the baseline total and LDL-C levels were lower in the groups with lower post-treatment LDL-C levels. All other characteristics were largely similar between groups (Table S1). Information on the names and doses of statins from the validation hospital cohort is shown in Table S2. Atorvastatin, rosuvastatin, and pitavastatin were used often, while atorvastatin 10 mg and rosuvastatin 10 mg were prescribed in 33.7 % and 22.6 %, respectively, in the cohort.

3.2. Composite events and mortality according to post-treatment LDL-C: nationwide cohort

Detailed data on the composite events and total mortality in the nationwide cohort are shown in Table 2. During follow-up (median: 7.5 years), the mean LDL-C of the total population decreased from 145 to 117 mg/dL (numeric percentage change: −19.3 %). The rates of composite events/1000 person-year in the total population was 8.38. Lower adjusted event risks were more evident in individuals with LDL-C levels <120 mg/dL compared to those with LDL-C levels ≥120 mg/dL after treatment (Table 2). When an LDL-C of ≥140 mg/dL was defined as the reference level in the spline regression model, the HR of composite events was significantly lower (from levels <115 mg/dL) (Fig. 2). Furthermore, lower risks of each event component were observed in individuals with post-treatment LDL-C levels <120 mg/dL. However, the mortality risk in patients with lower LDL-C levels after treatment did not significantly differ from that in the reference group (Table 2).

3.3. Composite events and mortality according to post-treatment LDL-C in men and women

Detailed data comparing the risks between men and women are presented in Table S2. Although the composite event risks did not significantly differ between men and women, the 95 % CIs of the first two LDL-C groups were < 1 only in men. The adjusted HRs for MI in the first two LDL-C groups were clearly lower in men than in women ($p = 0.042$). The adjusted HRs for coronary revascularization, ischemic stroke/TIA, and total mortality in each LDL-C group did not differ significantly between male and female patients. However, the 95 % CIs of coronary revascularization risk in the first two LDL-C groups were < 1 only in men (Table S3.

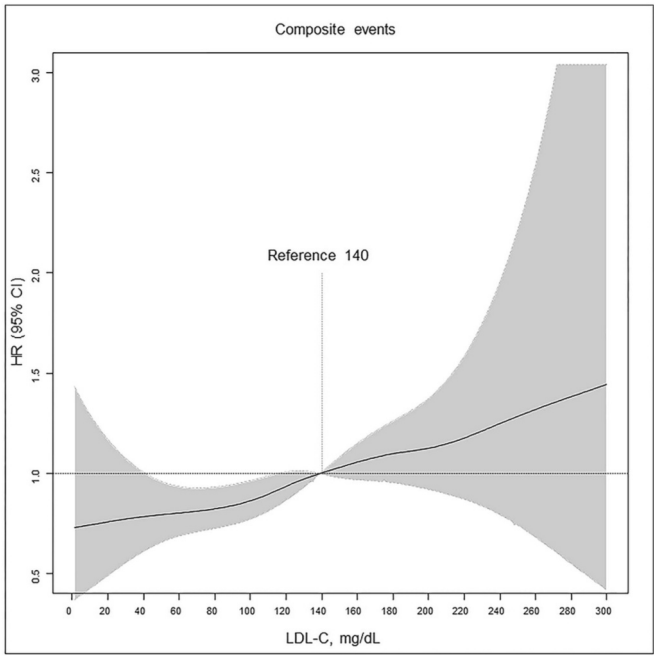

Fig. 2. Spline regression model of the hazard of composite events by post-treatment LDL-C levels. If an LDL-C level of ≥140 mg/dL was used as the reference level, the hazard ratio was significantly lower (non-overlapping 95 % CI) when an LDL-C level was <115 mg/dL.
LDL-C: low-density lipoprotein-cholesterol; CI, confidence interval.

3.4. Composite events and mortality according to post-treatment LDL-C: validation cohort

During follow-up (median: 8.7 years), the mean LDL-C level of the total population decreased from 147 to 92 mg/dL (numeric percentage change: −37.4 %). The rates of composite events/1000 person-year in the total population was 10.83. Lower adjusted risks were more obvious in individuals with LDL-C levels <100 mg/dL than in those with LDL-C levels ≥100 mg/dL after treatment (Table 3).

Adjusted HRs of MI and ischemic stroke/TIA in the first three LDL-C groups did not significantly differ from those of the reference group. Conversely, the lower risks of coronary revascularization in the groups with post-treatment LDL-C levels <100 mg/dL were more evident than the groups with post-treatment LDL-C levels ≥100 mg/dL. Adjusted HRs of total mortality in the first three groups were not significantly different from those of the reference group (Table 3).

4. Discussion

The major findings of the current study in the intermediate risk population are as follows: 1) in the nationwide cohort, lower composite event risk was more obvious in individuals with post-treatment LDL-C levels <120 mg/dL than those with LDL-C levels ≥120 mg/dL; 2) this trend was consistent for each event component (MI, coronary revascularization, and ischemic stroke/TIA); 3) the risk of total mortality showed no difference according to LDL-C levels after treatment; 4) men showed a lower risk of MI in the groups with lower post-treatment LDL-C, although the same gender difference was not significant for composite events; 5) in the tertiary hospital cohort, a lower event risk was more evident in the groups that achieved post-treatment LDL-C levels <100 mg/dL compared to that in other groups. To our knowledge, this is the first study to demonstrate the optimal LDL-C levels in individuals with intermediate cardiovascular risk. By providing evidence on cholesterol targets, this study may promote more efficient cardiovascular prevention in this group, which comprises a large proportion of the total population. In addition, these results are based on Northeast Asians, who have been infrequently included in large-scale prior studies on lipid-lowering therapy.

In our nationwide cohort, the overall composite event rate in the total population was 8.38/1000 person-years. Owing to the limited data availability, we included coronary revascularization rather than cardiovascular death in the composite events. However, cardiovascular death was included in clinical outcomes for latest guidelines on cardiovascular prevention in the United States [19] and Europe [4]. Even after considering this difference, the event rate in our study population was similar to that of intermediate-risk groups in major international guidelines. Nevertheless, as all our subjects were statin users, the 10-year event risk without pharmacotherapy may have been higher than 8.38 %.

The Heart Outcomes Prevention Evaluation-3 (HOPE-3) trial analyzed the effects of statins in a population with intermediate cardiovascular risk. If the composite event rate of the statin group in the HOPE-3 trial had been estimated according to the same event components as those in our nationwide cohort, the value would be 4.8 %/10-year which is lower than that of our cohort. The mean LDL-C levels before and after drug treatment in the HOPE-3 trial (128 and 88–93 mg/dL, respectively) were lower than those in our study. However, it is difficult to suggest optimal LDL-C levels from data collected in the HOPE-3 trial, as the differential clinical benefits of post-treatment LDL-C levels were not analyzed [10]. The estimated rate of the same composite events in the statin group in the Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese (MEGA) study [20] was 9.2 %/10-year, which is similar to our result. However, they only used low-dose pravastatin, and the post-treatment LDL-C level was 138 mg/dL. Therefore, in the MEGA study, it was difficult to confirm the additional benefit of achieving LDL-C levels <120 mg/dL, which was the cut-off in our study population at which patients exhibited a lower event risk. In the nationwide cohort of our study, lower event risk in participants with post-treatment LDL-C levels of 100–119 mg/dL was more pronounced than those with LDL-C levels ≥120 mg/dL. However, the risk of participants achieving LDL-C levels <100 mg/dL did not show a clear difference from that of participants with post-treatment LDL-C 100–119 mg/dL. Although the lack of a difference between the two groups with the lowest LDL-C levels in our study is uncertain, it is possibly due to a minimal event reduction by more aggressive lipid lowering in our intermediate-risk population. Conversely, our study was retrospective in nature, and the number of patients using intensive lipid-lowering therapy and achieving an LDL-C < 100 mg/dL may have been small. This could be a potential limitation of the clinical impact analysis of LDL-C reduction in the current study.

In our tertiary hospital cohort, lower event risk in patients with post-treatment LDL-C levels <100 mg/dL was more evident than patients with LDL-C levels ≥100 mg/dL. Based on this result, the optimal LDL-C level in the intermediate-risk group could be set as <100 mg/dL. The reason for the difference in results between the nationwide and tertiary hospital cohorts is not completely clear but could be explained in several ways. Although we included patients with the same criteria in the two cohorts, the event risk seemed modestly higher in the tertiary hospital cohort. In other words, the mean rates of composite events were 9.38 and 10.83/1000-person year in the nationwide and tertiary hospital cohorts, respectively. The mean age was 62.6 years in the tertiary hospital cohort, which was approximately 4 years more than that of the nationwide cohort. In addition, the rate of patients with at least three risk factors in the tertiary hospital cohort was 32.3 %, which was approximately 4 % higher than that in the nationwide cohort. In contrast, the mean LDL-C level reduction was 19.3 % in the nationwide cohort and 37.4 % in the tertiary hospital cohort. This difference in the validation cohort may be, at least partially, related to the higher consistency and adherence to lipid-lowering therapy. As the composite event rate was higher in the latter cohort, patients enrolled in this cohort may have been at higher risk than those in the nationwide cohort, even if

Table 3
Composite events and total mortality according to post-treatment LDL-C levels: the validation cohort[a].

Variables	Follow-up LDL-C, mg/dL	Number of patients	Events	Duration, person-year	Rate (/1000 person-year)	HR (95 % CI) (Model 1)	p	HR (95 % CI) (Model 2)	p
Composite events	Total	1859	149	13,755	10.83				
	<80	662	40	4453	8.98	0.59 (0.37, 0.93)	0.02	0.52 (0.33, 0.83)	0.006
	80–99	606	44	4561	9.65	0.63 (0.40, 0.99)	0.045	0.60 (0.38, 0.94)	0.03
	100–119	314	31	2512	12.34	0.81 (0.50, 1.32)	0.39	0.78 (0.48, 1.28)	0.33
	≥120	277	34	2230	15.24	1		1	
MI	Total	1859	26	14,800	1.76				
	<80	662	7	4716	1.48	0.54 (0.19, 1.54)	0.25	0.51 (0.17, 1.49)	0.22
	80–99	606	5	4860	1.03	0.37 (0.12, 1.17)	0.09	0.36 (0.11, 1.14)	0.08
	100–119	314	7	2750	2.55	0.90 (0.32, 2.58)	0.85	0.88 (0.31, 2.52)	0.81
	≥120	277	7	2474	2.83	1		1	
Coronary revascularization	Total	1859	90	14,168	6.35				
	<80	662	26	4568	5.69	0.68 (0.37, 1.23)	0.20	0.49 (0.26, 0.89)	0.02
	80–99	606	24	4697	5.11	0.62 (0.34, 1.13)	0.12	0.54 (0.29, 0.99)	0.045
	100–119	314	21	2577	8.15	0.99 (0.53, 1.85)	0.98	0.90 (0.48, 1.67)	0.73
	≥120	277	19	2327	8.17	1		1	
Ischemic stroke/TIA	Total	1859	82	14,499	5.66				
	<80	662	25	4640	5.39	0.75 (0.41, 1.38)	0.36	0.74 (0.39, 1.39)	0.35
	80–99	606	28	4748	5.90	0.80 (0.44, 1.45)	0.46	0.83 (0.45, 1.54)	0.56
	100–119	314	11 (3.5 %)	2721	4.04	0.54 (0.25, 1.14)	0.10	0.53 (0.25, 1.14)	0.11
	≥120	277	18 (6.5 %)	2390	7.53	1		1	
Total mortality	Total	1859	21 (1.1 %)	14,921	1.41				
	<80	662	4 (0.6 %)	4758	0.84	1.18 (0.21, 6.50)	0.85	1.17 (0.21, 6.54)	0.86
	80–99	606	10 (1.7 %)	4883	2.05	2.73 (0.60, 12.50)	0.20	3.04 (0.66, 14.01)	0.15
	100–119	314	5 (1.6 %)	2782	1.8	2.32 (0.45, 12.01)	0.31	2.50 (0.48, 13.05)	0.28
	≥120	277	2 (0.7 %)	2498	0.8	1		1	

LDL-C, low-density lipoprotein cholesterol; HR, hazard ratio; CI, confidence interval; MI, myocardial infarction; TIA, transient ischemic attack.
Model 1: unadjusted.
Model 2 was adjusted for age, sex, body mass index, hypertension, smoking, triglycerides, low-density lipoprotein cholesterol, and antiplatelet therapy.
p values are from Cox proportional hazard model.
[a] Median follow-up duration: 8.7 years.

the risks of both groups were classified as the same "intermediate." Collectively, the range of risk in individuals with intermediate risk may be wide, and the optimal LDL-C level in these patients could range from <100 to <120 mg/dL, according to their differential risk within the group.

In our nationwide cohort, total mortality did not differ according to post-treatment LDL-C levels. Previous primary prevention studies using populations with similar risks showed inconsistent results regarding total mortality [9,10,20]. Analyses of prior studies on primary prevention found a lower total mortality in the statin therapy group than in the control group, with a HR of 0.86 [7,21]. However, it is difficult to compare these results with ours, as the analyzed studies did not classify outcomes according to LDL-C levels. Notably, Chou et al. reported no differences in mortality based on statin intensity [21].

In our study, we found no significant difference between men and women in terms of the benefits of statins on cardiovascular events. In a meta-analysis of primary prevention studies, the benefits of statins or high-intensity statins on composite events were slightly smaller in female patients. However, in the subgroup analysis, the risk reduction by statin therapy was largely similar irrespective of sex in all groups, including those with the lowest 5-year risk of composite events of <10 % [22]. In another study analyzing individual event components, the risk reduction of MI and stroke was clearer in men [21]. However, in the two above-mentioned reports, no analysis of post-treatment LDL-C levels was performed.

The optimal LDL-C target we suggest from our results is <120 mg/dL derived from the nationwide cohort rather than <100 mg/dL derived from the hospital cohort. We think this target is more reasonable since the nationwide cohort is much larger than the validation hospital cohort and, thus, provides statistically stronger evidence. In the current study, pre-treatment LDL-C levels were similar between the two cohorts, but post-treatment levels were substantially lower in the validation cohort. Although it is difficult to identify a clear background of this finding, medication adherence might have influenced the results. Moreover, our results indicate the potential of further lipid lowering and greater clinical benefit in the group with higher adherence.

The fibrate use rates were about 1 % in the groups of our two cohorts. This rate was not appropriate for statistical analysis of their clinical impact. In addition, representative lipid-lowering agents targeting LDL-C, except statins, are ezetimibe and PCSK9 inhibitors. These two agents are generally recommended as add-on therapy to statins. However, our study did not address these agents, as they are rarely used in individuals

with intermediate cardiovascular risk.

Despite its strengths, our study has several limitations which should be considered. Firstly, the observational nature of this study may have limited its applicability; although we adjusted for as many clinical variables as possible when analyzing outcomes according to post-treatment LDL-C levels, this may have been insufficient. For example, lifestyle modifications are difficult to implement. However, we enrolled a large-scale population and validated the main results using a second cohort in an attempt to minimize errors and maximize evidence power. The composite events in this study included MI, coronary revascularization, and ischemic stroke/TIA, while cardiovascular death was not included. Data from the NHIS of Korea do not include the cause of death. Other studies have not always included unified components to define the outcomes, and this aspect of our research could be a hurdle when comparing with studies with a different definition. In addition, it is possible that a small number of patients with familial hypercholesterolemia who have high cardiovascular risk could have been included in the current study. Although we excluded individuals with LDL-C $\geq$ 190 mg/dL, some patients with this disease might have had lower cholesterol level than this value. However, our study is the first to provide evidence on treatment targets for intermediate-risk populations based on a focused analysis according to post-treatment LDL-C levels.

In conclusion, the results of this study showed that individuals with intermediate cardiovascular risk who achieved an LDL-C $<$ 120 mg/dL after statin therapy showed a lower composite event risk than those who did not. The present large-scale nationwide cohort study demonstrates, for the first time, the optimal LDL-C level after statin therapy. These findings provide clinically useful evidence on target LDL-C levels in this population and may help clinicians effectively promote cardiovascular prevention.

CRediT authorship contribution statement

JK, HK and SHP contributed equally to this work. KH and S-HL are joint senior authors and contributed to the conception and design of the work, interpretation of data, and critical revision of the manuscript. JK, HK, SHP, and YK contributed to the acquisition and analysis of data. JK, HK, SHP, and S-HL contributed to the drafting of the manuscript. All authors approved the final version and submission of the manuscript.

Declaration of competing interest

None.

Data availability

The data that support the findings of this study are available from the corresponding authors upon reasonable request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.metabol.2023.155723.

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