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Brief Report

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Impact of Severe Hypercholesterolemia on Cardiovascular Risk in Individuals With or Without Diabetes Mellitus

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ABSTRACT

Objective: The aim of the current study was to investigate whether the impact of low-density lipoprotein-cholesterol (LDL-C) levels on cardiovascular risk is different between individuals with severe hypercholesterolemia and diabetes mellitus (DM) and those without DM.
Methods: This study used the database of a National Health Insurance Service cohort of Korea. Among individuals who underwent health check-up, 2,261,332 were included and categorized into 3 groups with severe hypercholesterolemia, ≥260, 225–259, and 190–224 mg/dL groups, and a control group (<160 mg/dL). Risks of composite events (myocardial infarction [MI], coronary revascularization, and ischemic stroke) and total mortality were analyzed, according to the presence of DM.
Results: Of the study population, 5.2% had DM. During median follow-up of 6.1 years, the rates of composite events (/1,000 person-year) in non-DM and DM subjects were up to 5.66 and 8.92, respectively. Adjusted hazard ratios (aHRs) of the composite events ranged up to 3.11 and 1.44 in non-DM and DM groups, respectively (p<0.0001 between LDL-C categories in both groups). Dependency of aHR on LDL-C levels was more prominent in the non-DM group. aHRs of MI and coronary revascularization showed similar tendency to the composite events. Although aHRs of ischemic stroke (p<0.0001) and total mortality (p=0.002) were different according to LDL-C categories in the non-DM group, these relations were not observed in DM group.
Conclusion: Although individuals with severe hypercholesterolemia had high cardiovascular risk when DM was present, the impact of LDL-C on the risk was attenuated in this population.

Keywords: Outcome assessment, health care; Hyperlipoproteinemia type II; Coronary artery disease; Diabetes mellitus, type 2

INTRODUCTION

Familial hypercholesterolemia (FH) is global health burden.[1,2] It accompanies severe hypercholesterolemia and cause very high cardiovascular risk. Therefore, patient care for cardiovascular prevention is of critical importance.[3,4] Although these patients already have high low-density lipoprotein-cholesterol (LDL-C) levels, it is well-known that patients with further higher levels within this population show incrementally greater cardiovascular risk.[5]

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Conflict of Interest

The authors have no conflicts of interest to declare.

Author Contributions

Conceptualization: Lee SH; Data curation: Park S, Han K; Formal analysis: Park S, Han K; Funding acquisition: Lee SH; Investigation: Lee CJ, Park S, Han K, Lee SH; Methodology: Lee CJ, Han K; Project administration: Lee SH; Supervision: Lee SH; Writing - original draft: Lee CJ, Park S, Lee SH; Writing – review & editing: Han K, Lee SH.

Diabetes mellitus (DM) is also a crucial risk factor of cardiovascular disease.[6] Cardiovascular prevention is also important in this population.[7] Some international guidelines consider the presence of DM or DM-associated complications directly to upgrade cardiovascular risk status.[8] Therefore, there are efforts to understand and predict cardiovascular risk in patients with DM separately, and utilize the results in clinical management.[7]

The aim of the current study was to investigate whether the impact of LDL-C levels on cardiovascular risk is different between individuals with severe hypercholesterolemia and DM and those without DM. We analyzed cardiovascular risk in this population with or without DM and compared the impact of LDL-C on cardiovascular events and total mortality.

MATERIALS AND METHODS

This study was conducted according to the Declaration of Helsinki and the study protocol was approved by Institutional Review Board of Severance Hospital, Yonsei University College of Medicine (4-2019-0516) and National Health Insurance Service (NHIS) of Korea (NHIS-2020-4-160). All study population of the present study overlap with statin non-users of our previous study.[9] As NHIS database has been built for public use of health screening data with deidentified information, requirement for informed consent was waived. The data supporting the findings of the current study are available from the corresponding author upon reasonable request. We performed the present study in accordance with STROBE guidelines.

1. Database and study population

This is a retrospective cohort study using database of the NHIS, Korea[9] including demographic data, diagnoses by the International Classification of Diseases Tenth Revision, Clinical Modification (ICD-10). The database also contains use of in- and outpatient services, pharmacy claims, and mortality. The NHIS, Korea provides health examination every other year for all Korean adults aged ≥20 years. It includes self-questionnaires on medical history, physical examination, and blood tests such as lipid profile. These results are included in the database anonymously.

The enrollment flow of study population is shown in **Fig. 1**. Individuals who received the first NHIS health examination between January and December 2009 were initially screened. Among them, those who took ≥ one follow-up examination were identified. Last follow-up was performed in December 2018. The exclusion criteria were prior cardio- or cerebrovascular disease, prior statin use, no regular follow-up health examination, missing laboratory values, suspicious errors in cholesterol levels, starting statins at time point between 0–1-year follow-up, or death or cardio-/cerebrovascular events at <1-year follow-up. Finally, 2,261,332 persons were enrolled.

The study population were categorized by LDL-C levels, that are as follows: ≥260, 225–259, 190–224, and <160 mg/dL. The 260 mg/dL level is from the American Make Early Diagnosis to Prevent Early Death criteria for FH aged ≥40 years.[10] This age range is that of most study subjects in our cohort. The 225 mg/dL level is from the LDL-C threshold for carriers of putative FH-associated mutations from our prior study.[2] The 190 mg/dL level is from the cut-off value of severe hypercholesterolemia in recent American guidelines for lipid-lowering therapy.[11] As LDL-C ≥160 mg/dL is regarded "high,"[12] individuals with LDL <160 mg/dL was used as a reference group.

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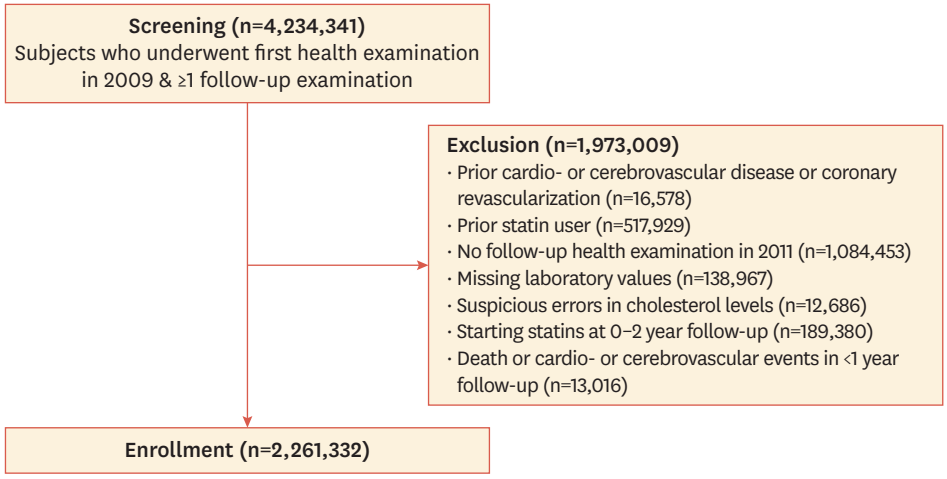

Fig. 1. Enrollment flow of study population.

2. Definitions

DM, hypertension, and body mass index (BMI) were assessed as clinical characteristics. The smoking status was checked based on self-questionnaires. Blood samples for lipid profiles were collected after overnight fasting, and the levels were assayed using an enzymatic measurement. DM and hypertension were defined as diagnosis history (ICD-10) and use of more than one anti-diabetic or anti-hypertensive agents, respectively.

The primary outcome variable was composite of myocardial infarction (MI), coronary revascularization, and ischemic stroke. The secondary outcome variables were each component of primary outcome variable and total mortality. MI was defined according to ICD-10 codes (I12–I22) during hospitalization or these diagnostic codes found at least 2 times in the outpatient records. Coronary revascularization was defined as percutaneous coronary intervention or coronary artery bypass graft. The former included the codes M655*–M657* and the latter included the codes OA631*–OA639*, OB631*–OB639*, OA641*, OA642*, O0161*–O0171*, and O1641*–O1647*. Ischemic stroke was identified by ICD-10 codes during hospitalization and claims for brain imaging studies. Total mortality was assessed by those included in the NHIS linked to data provided by Statistics Korea.

3. Statistical analysis

Continuous variables were checked for normality using Shapiro-Wilk normality test. Those with normal distribution are presented as mean ± standard deviation and those with non-normal distribution as median (interquartile range). Categorical variables were presented as numbers (percentage). Continuous and categorical variables in subject groups were compared using Student's *t*-test and χ^2 test, respectively. Cox proportional hazards models were used to analyze the association between groups categorized by baseline LDL-C levels and primary and secondary outcome variables. Hazard ratios (HRs) and 95% confidence intervals were calculated in an unadjusted model 1. In model 2, 7 pre-specified potential confounders were adjusted as follows: age, sex, BMI, hypertension, smoking, triglyceride, and antiplatelet agent. Study population were analyzed according to the presence of DM.

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RESULTS

1. Baseline characteristics

More than half of study population were under age of 50 (63.1%) and males were 60.2%. About 5% of the patients had DM (**Table 1**). Mean LDL-C levels were 110 mg/dL. Individuals with LDL-C >260, 225–259, 190–224, <160 mg/dL were 426, 1,762, 17,557, and 2,016,516, respectively. These corresponded to 0.02%, 0.08%, 0.8%, and 89.2% of total study population, respectively (**Table 2**).

2. Composite events in individuals with different LDL-C categories according to DM: primary outcome variable

The rates of composite events, the primary outcome variable, were up to 5.66/1,000 person-year in the non-DM group, whereas these were up to 8.92/1,000 person-year in the DM group. Adjusted HRs (aHRs) for composite events were up to 3.11 (p<0.0001 for comparison between LDL-C categories) in the non-DM group. The aHRs for the events were up to 1.44 (p<0.0001) in the DM group. Higher aHRs in individuals with higher LDL-C were more obviously observed in the non-DM group (**Table 2** and **Fig. 2**).

3. Each cardiovascular event and total mortality in individuals with different LDL-C categories according to DM: secondary outcome variables

The rates of MI were up to 3.09/1,000 person-year in the non-DM group, whereas these were up to 4.76 in the DM group. aHRs differed between individuals according to their LDL-C categories (p<0.0001 in both non-DM and DM groups) and the risk tended to be higher in individuals with higher LDL-C categories (up to 5.96 and 2.94 in non-DM and DM groups, respectively). Dependency of aHR on LDL-C levels was more prominent in the non-DM group. aHRs of coronary revascularization were up to 5.34 and 2.75 in the non-DM and DM groups, respectively, and showed similar tendency to MI (p<0.0001 for comparison between LDL-C categories). aHRs of ischemic stroke were up to 1.92 in the non-DM group according to LDL-C categories (p<0.0001). In patients with DM, interestingly, aHR between individuals with differing LDL-C categories did not show significant difference (p=0.23) (**Table 2** and **Fig. 2**).

Table 1. Clinical characteristics of the study population

Variables	Grouping by LDL-C levels (mg/dL)											
	>260			225–259			190–224			<160		
	Non-DM (n=426)	DM (n=61)	p	Non-DM (n=1,762)	DM (n=174)	p	Non-DM (n=17,557)	DM (n=1,287)	p	Non-DM (n=2,016,517)	DM (n=109,350)	p
Age	45.2±13.2	53.1±14.4	<0.0001	47.6±12.8	42.2±12.1	<0.0001	48.0±12.33	52.8±12.9	<0.0001	45.0±12.9	55.4±12.5	<0.0001
Male	179 (42.0)	25 (41.0)	0.88	795 (45.1)	74 (42.5)	0.51	10,500 (59.8)	803 (62.4)	0.067	1,197,817 (59.4)	80,379 (73.5)	<0.0001
Medical history												
Hypertension	92 (21.6)	25 (41.0)	<0.0009	339 (19.2)	67 (38.5)	<0.0001	3,569 (20.3)	538 (41.8)	<0.0001	343,800 (17.1)	51,107 (46.7)	<0.0001
Current smoker	137 (32.2)	21 (34.4)	0.72	503 (28.6)	43 (24.7)	0.28	5,214 (29.7)	383 (29.8)	0.96	54,755 (27.2)	33,518 (30.6)	<0.0001
BMI (kg/m^2)	24.6±3.5	25.5±3.4	0.061	24.9±3.2	25.6±3.7	0.007	24.9±3.1	25.6±3.4	<0.0001	23.4±3.1	24.7±3.3	<0.0001
Lipid profile (mg/dL)												
TC	393±89	437±184	0.002	319±22	326±27	<0.0001	282±19	288±22	<0.0001	188±29	189±31	<0.0001
TG	133 (92–192)	192 (122–275)	0.002	133 (98–180)	160 (112–216)	<0.0004	126 (93–171)	151 (113–208)	<0.0001	102 (70–151)	137 (93–204)	<0.0001
HDL-C	55.2±16.7	74.4±119	0.002	55.0±13.8	55.6±17.4	0.59	54.1±17.3	53.1±12.6	0.046	55.8±20.9	51.1±25.0	<0.0001
LDL-C	306±81	332±85	0.15	236±9	237±9	0.54	201±9	201±9	0.021	108±26	105±28	<0.0001
Antiplatelet agent	13 (3.1)	4 (6.6)	0.16	49 (2.8)	12 (6.9)	0.003	552 (3.1)	132 (10.3)	<0.0001	71,320 (4.0)	21,370 (19.5)	<0.0001

Data are presented as number (%), mean ± standard deviation or median (interquartile range) unless defined otherwise.
DM, diabetes mellitus; BMI, body mass index; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol.

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Table 2. Risk of composite cardiovascular events and total mortality in the patient groups classified by LDL-C levels and DM without statin therapy

Variables	LDL-C (mg/dL)	No. of patients	Events	Duration (person-year)	Rate (/1,000 person-year)	HR (95% CI) (model 1)	*p*	HR (95% CI) (model 2)	*p*
Composite events									
Non-DM	>260	426	11	1,942	5.66	3.20 (1.77–5.77)	<0.0001	3.11 (1.73–5.61)	<0.0001
	225–259	1,762	35	7,923	4.42	2.50 (1.79–3.48)		2.22 (1.59–3.09)	
	190–224	17,557	310	81,748	3.79	2.14 (1.91–2.40)		1.84 (1.65–2.06)	
	<160	2,016,516	21,836	12,134,516	1.80	1		1	
DM	>260	61	2	257	7.79	0.98 (0.25–3.93)	0.27	1.08 (0.27–4.31)	<0.001
	225–259	174	5	628	7.96	1.01 (0.42–2.44)		1.28 (0.53–3.07)	
	190–224	1,287	44	4,932	8.92	1.13 (0.84–1.52)		1.44 (1.07–1.93)	
	<160	109,349	4,282	538,124	7.96	1		1	
MI									
Non-DM	>260	426	6	1,944	3.09	6.29 (2.83–14.00)	<0.0001	5.96 (2.69–13.23)	<0.0001
	225–259	1,762	16	7,932	2.02	4.12 (2.52–6.73)		3.52 (2.16–5.75)	
	190–224	17,557	118	81,822	1.44	2.94 (2.45–3.53)		2.46 (2.05–2.95)	
	<160	2,016,516	6,114	12,147,769	0.50	1		1	
DM	>260	61	0	257	0	-	0.0002	-	<0.0001
	225–259	174	3	631	4.76	2.44 (0.78–7.67)		2.84 (0.91–8.83)	
	190–224	1,287	17	4,939	3.44	1.74 (1.08–2.82)		2.12 (1.31–3.42)	
	<160	109,349	1,089	540,691	2.01	1		1	
Coronary revascularization									
Non-DM	>260	426	6	1,518	3.95	5.63 (2.35–13.50)	<0.0001	5.34 (2.22–12.84)	<0.0001
	225–259	1,762	21	6,171	3.40	5.54 (3.58–8.59)		4.94 (3.18–7.66)	
	190–224	17,557	150	64,271	2.33	3.35 (2.81–4.00)		2.89 (2.42–3.45)	
	<160	2,016,516	6,988	10,134,871	0.69	1		1	
DM	>260	61	0	196	0	-	0.023	-	<0.0001
	225–259	174	3	457	6.57	2.23 (0.72–6.92)		2.75 (0.89–8.54)	
	190–224	1,287	21	3,660	5.74	1.29 (0.76–2.18)		1.61 (0.95–2.72)	
	<160	109,349	1,541	431,613	3.57	1		1	
Ischemic stroke									
Non-DM	>260	426	4	1,942	2.06	2.03 (0.76–5.41)	<0.0001	1.92 (0.72–5.10)	<0.0001
	225–259	1,762	14	7,926	1.77	1.74 (1.03–2.94)		1.55 (0.92–2.62)	
	190–224	17,557	143	81,774	1.75	1.72 (1.46–2.03)		1.48 (1.26–1.75)	
	<160	2,016,516	12,492	12,140,173	1.03	1		1	
DM	>260	61	2	257	7.79	1.73 (0.43–6.93)	0.91	1.82 (0.45–7.27)	0.23
	225–259	174	2	628	3.18	0.72 (0.18–2.87)		0.92 (0.23–3.67)	
	190–224	1,287	20	4,940	4.05	0.91 (0.59–1.41)		1.16 (0.75–1.80)	
	<160	109,349	2,426	539,005	4.50	1		1	
Total mortality									
Non-DM	>260	426	10	1,944	5.14	2.00 (1.08–3.72)	0.026	2.26 (1.22–4.21)	0.002
	225–259	1,762	23	7,934	2.90	1.13 (0.75–1.70)		1.19 (0.79–1.79)	
	190–224	17,557	240	81,841	2.93	1.14 (1.01–1.30)		1.10 (0.97–1.25)	
	<160	2,016,516	31,933	12,152,607	2.63	1		1	
DM	>260	61	5	257	19.45	1.86 (0.78–4.48)	0.0001	2.22 (0.92–5.33)	0.25
	225–259	174	7	631	11.10	1.09 (0.52–2.29)		1.50 (0.71–3.15)	
	190–224	1,287	39	4,947	7.88	0.77 (0.56–1.05)		1.13 (0.82–1.55)	
	<160	109,349	5,730	541,341	10.58	1		1	

Model 1: unadjusted. Model 2: adjusted for age, sex, body mass index, diabetes mellitus, hypertension, smoking, triglyceride, antiplatelet agent. Composite events: MI, coronary revascularization, or ischemic stroke. The *p* values are from Wald test for HRs of patient groups.
LDL-C, low-density lipoprotein-cholesterol; DM, diabetes mellitus; HR, hazard ratio; CI, confidence interval; MI, myocardial infarction.

The rates of mortality were up to 5.14 and 19.45 in the non-DM and DM groups, respectively. aHR of total mortality were up to 2.26 in the non-DM groups and revealed difference between individuals with different LDL-C categories (p=0.002). Although adjusted mortality risk were up to 2.22 in the DM group, difference between individuals with differing LDL-C categories was not significant (p=0.25) (**Table 2** and **Fig. 2**).

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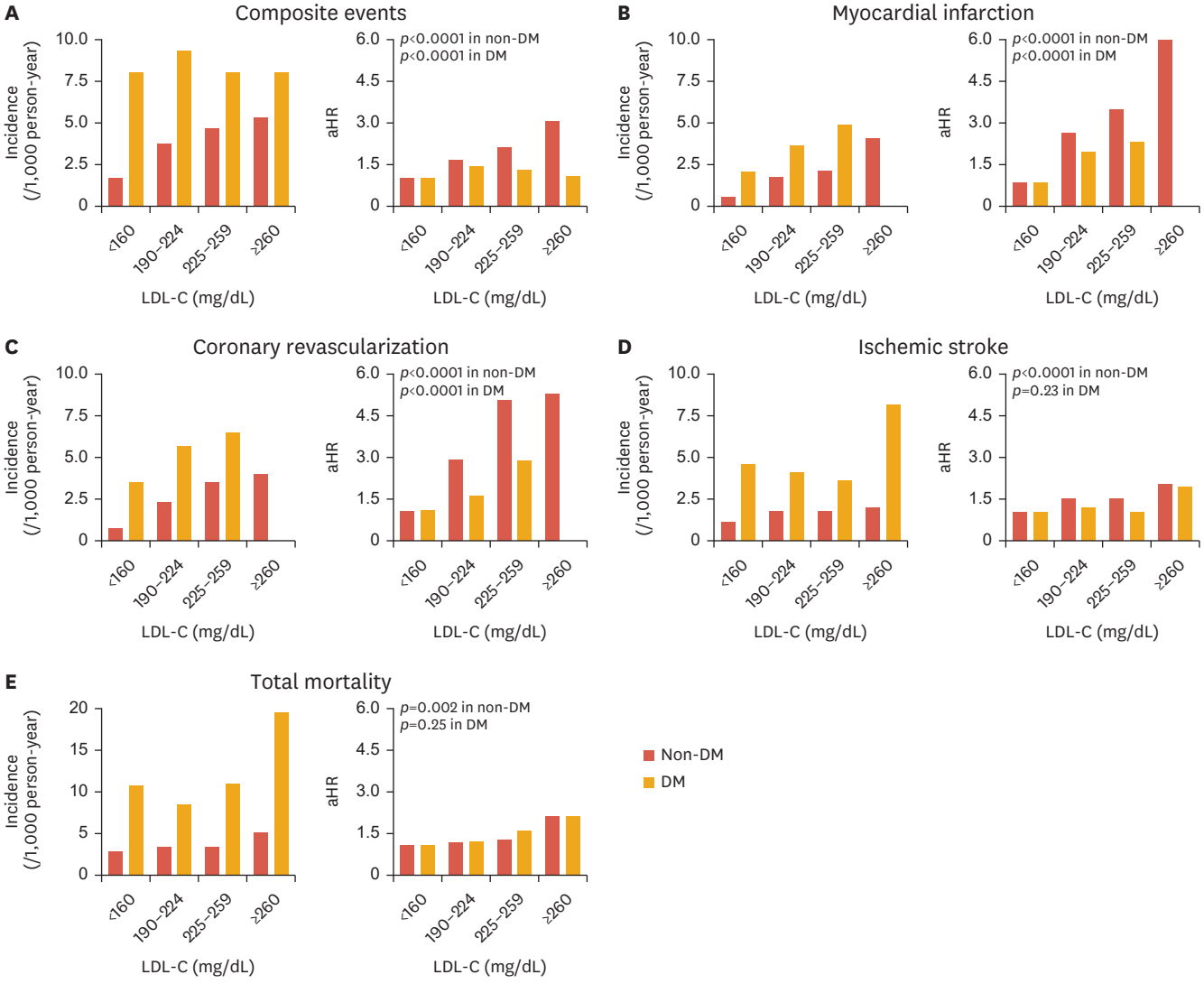

Fig. 2. Incidence of outcome variables and aHRs. (A) Composite events. (B) Myocardial infarction. (C) Coronary revascularization. (D) Ischemic stroke. (E) Total mortality.
aHR, adjusted hazard ratio; DM, diabetes mellitus; LDL-C, low-density lipoprotein-cholesterol.

DISCUSSION

The major findings of the present study include: 1) The cardiovascular event rates were consistently and considerably higher regardless of LDL-C categories in the DM group than in non-DM group. 2) Although a few variables did not show statistically significant difference, the LDL-C-dependent aHRs of most outcome variables tended to be lower in the DM group. 3) Although coronary artery disease (CAD)-related outcome variables were affected by LDL-C categories in the DM group, LDL-C levels did not have significant impact on the risk of ischemic stroke or total mortality in this group.

We analyzed relative risk associated with LDL-C levels in individuals without and with DM separately. As presented in **Table 2**, aHRs of composite events were up to 3.11, whereas these were up to 1.44 according to LDL-C levels in those without and with DM, respectively. We expressed this tendency of smaller elevation of HR from higher LDL-C in DM patients as

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"impact of LDL-C was attenuated in DM." Studies regarding whether the impact of LDL-C on cardiovascular outcomes is attenuated in patients with DM have been highly limited. In a Korean study using DM patients, DM duration, hypertension, smoking, family history of CAD but not LDL-C levels have been identified as predictors of the presence of CAD.[13] In a study performed in Sweden, the impact of LDL-C level on mortality or stroke risk was lower than those of smoking, physical activity, control of DM, and blood pressure. However, LDL-C levels revealed substantial effect on MI in individuals with DM.[7] In that study, LDL-C was one of top 3 factors for MI. Other high-ranked factors included glycated hemoglobin levels, systolic blood pressure, physical activity, and smoking. This finding is in accordance with our results that exhibited LDL-C level had influence on CAD-related risk in the DM group. Conversely, the impact of other cardiovascular risk factors such as low high-density lipoprotein-cholesterol (HDL-C) levels or triglyceride/HDL-C ratio could be attenuated in individuals with DM.[14] Collectively, the increase of relative risk by higher LDL-C level on stroke and total mortality seems not significant in patients with DM, the presence of DM can cause risk elevation regarding CAD-related events.

It is not completely clear what underlies the lack of association between LDL-C and ischemic stroke or total mortality in patients with DM. A few points could be discussed as follows. As mentioned in a prior study analyzing patients with DM, the impact of LDL-C on ischemic stroke or total mortality could be minimal compared to other risk factors.[7] In addition, absolute values of relative risk associated with higher LDL-C on ischemic stroke and total mortality were smaller than those on coronary events in the current study and a previous report.[9] This could have further attenuated the effect of LDL-C on these 2 outcomes.

The factors elevating cardiovascular risk in patients with FH have been reported as LDL-C levels, age, history of atherosclerotic cardiovascular disease, obesity, hypertension, and smoking.[5] In this study, DM did not affect the risk. Hypertension and low HDL-C were identified as predictors of CAD in the Korean FH registry study.[15] However, results on a neutral effect of DM need to be interpreted cautiously, as the populations of above-mentioned studies were relatively young and the prevalence of DM was small. These factors could have influenced the negative findings. In the current study, cardiovascular risk indicated by aHR was higher when DM was present in individuals with LDL-C ≥190 mg/dL, suggesting an impact of DM on the risk. As our study population was very large, the current finding on the effect of DM seems more persuasive than others.

In our study, event rates were considerably higher in patients with DM than that of the non-DM group. For instance, the composite event rate in the DM group even with LDL-C <160 mg/dL was higher than that in non-DM group with LDL-C ≥260 mg/dL. With regard to other event components, event rates of the DM group with normal LDL-C levels was similar or higher than those of non-DM group with ≥190 mg/dL or even ≥260 mg/dL. In this regard, DM itself is be a strong cardiovascular risk factor. In addition, incremental risk elevation by severe hypercholesterolemia in this people may be attenuated by some reason that remains to be elucidated.

Our study is not without limitations. We cannot completely explain the reason why the impact of LDL-C level on clinical outcome is attenuated in patients with DM. However, it is worth to note that our study analyzed a large cohort of severe hypercholesterolemia that has not been well studied and compared the DM and non-DM groups. Especially, we demonstrated minimal effect of LDL-C levels on stroke and total mortality in the study

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population and this may have a strong power as evidence. Furthermore, we validated that impact of LDL-C levels was greater for CAD-related events than for others.

In conclusion, although individuals with severe cholesterolemia had higher cardiovascular risk when DM was present, the impact of LDL-C on the risk was attenuated in this population. These results may help physicians to comprehensively control multiple risk factors in these patients at high risk.

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