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Original Research

Escalating Lipid Therapy After Achieving LDL-C <70 mg/dL With Moderate-Intensity Statins in High-Risk Patients

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AUTHOR'S SUMMARY

The benefit of escalating lipid-lowering therapy (LLT) after achieving target low-density lipoprotein-cholesterol levels with moderate-intensity statins in high-risk patients has not yet been reported. The current study demonstrated similar hard cardiovascular events and all-cause death, the primary outcomes, after LLT escalation in this context with atherosclerotic cardiovascular disease. However, the rate of secondary outcome, including coronary/peripheral revascularization, was lower in the escalation group.

ABSTRACT

Background and Objectives: Guidelines recommend target levels of low-density lipoprotein cholesterol (LDL-C) and intensive lipid-lowering therapy (LLT) in high-risk patients. However, the value of escalating LLT when the LDL-C targets are achieved with moderate-intensity statins is unknown. We aimed to evaluate the benefits of LLT escalation in this population.
Methods: In this retrospective propensity score-matched study, we screened data from two university hospitals between 2006 and 2021. Of the 54,069 patients with atherosclerotic cardiovascular disease (ASCVD), 3,205 who achieved LDL-C levels <70 mg/dL with moderate-intensity statins were included. After 1:3 matching, 1,315 patients (339 with LLT escalation and 976 without) were ultimately examined. The primary outcomes were major adverse cardiovascular and cerebrovascular events (MACCE)1 (cardiovascular death, nonfatal myocardial infarction, and nonfatal ischemic stroke) and all-cause death.
Results: During a median follow-up of 5.7 years, the MACCE1 rate was not significantly lower in the escalation group than in the non-escalation group (9.8 and 14.3/1,000 person-years, respectively; hazard ratio [HR], 0.68; 95% confidence interval [CI], 0.43–1.09; p=0.11). Kaplan–Meier curves showed similar results (log-rank p=0.11). The risk of all-cause death did not differ between the groups. MACCE2 rate, which additionally includes coronary/peripheral revascularization, was lower in the escalation group (24.5 and 35.4/1,000 person-years, respectively; HR, 0.70; 95% CI, 0.52–0.94; p=0.017).
Conclusions: LLT escalation did not significantly lower hard cardiovascular outcomes and all-cause death in patients with ASCVD achieving LDL-C levels <70 mg/dL with moderate-

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Conflict of Interest

The authors have no financial conflicts of interest.

Data Sharing Statement

Data supporting the results of this study are available from the corresponding authors upon reasonable request.

Author Contributions

Conceptualization: Lee SH; Data curation: Park G; Formal analysis: Park G; Funding acquisition: Lee SH; Investigation: Park G; Methodology: Lee SH; Project administration: Choi EY, Lee SH; Resources: Choi EY, Lee SH; Software: Lee SH; Supervision: Choi EY, Lee SH; Visualization: Park G; Writing - original draft: Park G, Lee SH; Writing - review & editing: Choi EY, Lee SH.

intensity statins. However, it had benefit in reducing revascularization rates in this population.

Keywords: Coronary artery disease; Dyslipidemias; Outcome assessment, health care; Hydroxymethylglutaryl-CoA reductase inhibitors

INTRODUCTION

Lipid-lowering therapy (LLT) is a cornerstone of cardiovascular prevention, with research on the appropriate LLT intensity steadily progressing.[1-3] However, physicians do not always strictly follow LLT guidelines in clinical practice.[4)5)] The latest guidelines on LLT recommend a low-density lipoprotein cholesterol (LDL-C) target of either <55 mg/dL[6)] or <70 mg/dL and a 50% reduction with high-intensity statins[7)] for patients with atherosclerotic cardiovascular disease (ASCVD). These targets are based on recently published outcome trials, including Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT),[8)] Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER),[9)] and Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab (ODYSSEY Outcomes).[10)] In these trials, individuals who received additional LLT on top of statins showed a follow-up LDL-C level <55 mg/dL and reduced cardiovascular risk. Notably, the mean LDL-C levels before additional LLT in these trials were 94, 92, and 92 mg/dL, respectively, which are substantially higher than the target levels recommended by current guidelines. In such cases, most physicians would consider LLT escalation.

In contrast, in clinical practice, LLT may not be further intensified when the LDL-C levels are <70 mg/dL. The American guidelines recommend high-intensity statins for high-risk conditions such as ASCVD.[7)] However, if LDL-C levels decrease to <70 mg/dL after using moderate-intensity statins instead of high-intensity statins, physicians may hesitate to escalate LLT. In particular, evidence regarding the clinical benefit of LLT escalation is lacking in this clinical context. Furthermore, the European LDL-C target of <55 mg/dL[6)] is not based on data showing the benefit of LLT escalation in patients who achieved LDL-C levels <70 mg/dL after statin therapy. Clarifying this issue will help guide clinical decision-making to allow patients to achieve the greatest cardiovascular benefits.

Therefore, in patients who achieved an LDL-C level <70 mg/dL using moderate-intensity statins, we compared the clinical outcomes of those who received LLT escalation with those of patients who did not. Thus, we aimed to determine whether LLT escalation was beneficial in this population. The primary purpose was to compare major cardiovascular and cerebrovascular adverse event (MACCE)1 composed of hard cardiovascular outcomes, and all-cause death. MACCE2 that additionally included revascularizations was secondarily compared.

METHODS

Ethical statement

This study was approved by the Institutional Review Board of Severance Hospital, Seoul, Korea (4–2023-0253) and was performed in accordance with the Declaration of Helsinki (2013). The requirement for obtaining informed consent was waived owing to the

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retrospective study design, and data of the study participants were de-identified according to confidentiality guidelines.

Study population

This was a retrospective study that used propensity score matching; the patients were screened from two university hospitals. We screened consecutive patients aged ≥18 years between January 2006 and December 2021 based on the following inclusion criteria: a diagnosis of ASCVD and 2–12 months of treatment with low- or moderate-intensity statins, as defined by the 2013 American College of Cardiology/American Heart Association guidelines.[3)11-13)] The diagnosis of ASCVD included coronary artery disease (CAD), ischemic stroke or transient ischemic attack, carotid artery stenosis, or peripheral artery disease. Patients with the following conditions were excluded: LDL-C level ≥70 mg/dL after low- to moderate-intensity statin use, lack of clinical or laboratory data, inconsistent statin use or dose after the study enrollment point, and misdiagnosis of ASCVD. The study enrollment point was defined as the time at which an LDL-C level <70 mg/dL was achieved after low- to moderate-intensity statin use. In patients with escalated LLT, regimens were escalated immediately (≤7 days) after achieving the LDL-C level. LLT escalation involved either an increase in statin dose or the addition of ezetimibe. LLT for ≥80% of the follow-up period was regarded as consistent.

A total of 54,069 screened patients had ASCVD and were treated with low- to moderate-intensity statins. After excluding patients with LDL-C ≥70 mg/dL after therapy (n=27,197) and those meeting the other exclusion criteria, 3,205 patients (355 with LLT escalation and 2,850 without LLT escalation after enrollment point) were included in this study. Using 1:3 propensity score matching, 1,315 patients (339 with LLT escalation and 976 without) were analyzed using clinical outcome data up to October 2023 (**Figure 1**). All patients received standard medical therapy and were followed up at outpatient clinics every 3–6 months.

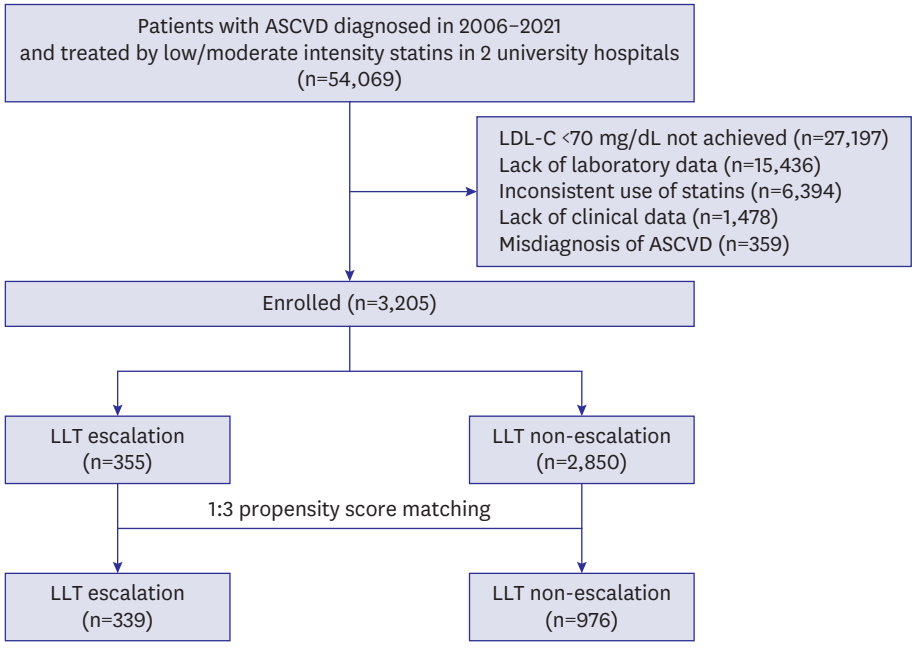

Figure 1. Flowchart of patient enrollment.
ASCVD = atherosclerotic cardiovascular disease; LDL-C = low-density lipoprotein cholesterol; LLT = lipid-lowering therapy.

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Outcome measures

We collected demographic data, medical history, laboratory data, and statin information from the medical records. Heart failure and atrial fibrillation were defined based on the corresponding International Classification of Diseases, Tenth Revision codes,[14] whereas chronic kidney disease was defined as an estimated glomerular filtration rate <60 mL/min/1.73 m^2. Routine blood samples were collected after fasting ≥8 hours.

The primary outcome variables were MACCE1 and all-cause death. MACCE1 was defined as the composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal ischemic stroke. The secondary outcomes were MACCE2, which additionally includes coronary and peripheral revascularization, and the individual components of MACCE2. Information on dates and causes of death was collected from the Korean Statistical Information Service and Statistics Korea. MACCE data were obtained by reviewing hospital records.

Statistical analysis

Categorical variables are presented as frequencies (percentages) and were compared using the χ^2 test. Continuous variables are reported as mean ± standard deviation or median (interquartile range). These were analyzed using the Shapiro–Wilk test for normality and, based on the results, compared using Student's t-test or the Wilcoxon rank-sum test.
We conducted 1:3 propensity score matching using the nearest neighbor method, with a caliper of 0.01 to reduce the effect of selection bias and potential confounders. The following variables, which could influence atherosclerotic cardiovascular event, were used for matching: age, sex, hypertension, diabetes mellitus, smoking history, acute coronary syndrome, ischemic stroke/transient ischemic attack, body mass index, multivessel coronary disease, triglyceride levels, and high-density lipoprotein cholesterol (HDL-C) levels at study enrollment. Matching was validated based on the standardized mean difference of the covariates, with a threshold of <0.1 indicating balanced matching. The distribution of propensity scores before and after matching is provided in **Supplementary Figure 1**. The rate of outcome variables was calculated by dividing the number of events by person-years at risk and reported as incidence/1,000 person-years. The cumulative incidence of the outcomes was assessed using Kaplan–Meier curves and compared using the log-rank test. Using Cox proportional hazards regression, we obtained the hazard ratio (HR) and 95% confidence interval (CI) for the outcome variables. Factors associated with MACCE1 were identified using a univariate Cox regression analysis. All variables used in the univariate analyses were included in the multivariate Cox proportional hazards analyses. We performed subgroup analyses of MACCE1 stratified by age, sex, and other major clinical variables. Interaction tests were conducted for all subgroups. All tests were two-tailed, with a significance level of <0.05. R version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria) was used for statistical analyses.

RESULTS

Baseline characteristics

Characteristics of the 1,315 patients (339 with LLT escalation and 976 without) are presented in **Table 1**. The mean age was 64 years, and 75% of the participants were male. The prevalence of cardiovascular risk factors was well-matched between the 2 groups. The majority of patients with ASCVD in the analyzed population had stable CAD, and more than half of those with CAD had multivessel involvement. The median LDL-C levels at enrollment were 58 and 57 mg/dL in the escalation and non-escalation groups, respectively. Nearly all the patients

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Table 1. Baseline characteristics of the study population after propensity score matching

Characteristics	Before matching				After matching			
	Escalation (n=355)	Non-escalation (n=2,850)	p value	SMD (%)	Escalation (n=339)	Non-escalation (n=976)	p value	SMD (%)
Age (years)	63.8±10.1	65.2±10.6	0.02	13.3	64.1±10.0	64.2±10.4	0.77	1.8
Male	270 (76.1)	2,056 (72.1)	0.14	8.9	256 (75.5)	736 (75.4)	>0.99	0.2
Medical history								
Hypertension	180 (50.7)	1,472 (51.6)	0.78	1.9	171 (50.4)	497 (50.9)	0.93	1.0
Diabetes mellitus	131 (36.9)	941 (33.0)	0.16	8.2	123 (36.3)	341 (34.9)	0.70	2.8
Smoking	137 (38.6)	1,062 (37.3)	0.34	8.5	127 (37.4)	385 (39.6)	0.75	1.1
Chronic kidney disease	13 (3.7)	133 (4.7)	0.47	5.0	12 (3.5)	47 (4.8)	0.41	6.4
Atrial fibrillation	15 (4.2)	190 (6.7)	0.10	10.8	15 (4.4)	59 (6.0)	0.33	7.3
Heart failure	20 (5.6)	162 (5.7)	>0.99	0.2	19 (5.6)	56 (5.7)	>0.99	0.6
Body mass index (kg/m^2)	24.5±3.1	24.3±3.0	0.32	5.6	24.5±3.1	24.4±3.1	0.52	4.1
Category of ASCVD								
Stable CAD	251 (70.7)	1,835 (64.4)	0.02	13.5	241 (71.1)	681 (69.8)	0.70	2.9
Acute coronary syndrome	57 (16.1)	433 (15.2)	0.73	2.4	55 (16.2)	155 (15.9)	0.95	0.9
Stroke or TIA	28 (7.9)	445 (15.6)	<0.001	24.2	27 (8.0)	84 (8.6)	0.80	2.3
Carotid stenosis	6 (1.7)	25 (0.9)	0.24	7.2	5 (1.5)	11 (1.1)	0.84	3.1
Peripheral artery disease	13 (3.7)	112 (3.9)	0.92	1.4	11 (3.2)	45 (4.6)	0.83	7.0
Number of diseased vessels in CAD			0.004	19.9			0.75	4.9
≥2	198 (55.8)	1,400 (49.1)			188 (55.5)	529 (54.2)		
1	110 (31.0)	868 (30.5)			108 (31.9)	307 (31.5)		
Lipid profiles at enrollment (mg/dL)								
Total cholesterol	121 (109–135)	121 (110–132)	0.38	7.0	121 (109–134)	120 (109–130)	0.19	8.6
Triglyceride	106 (76–151)	96 (73–131)	0.001	18.0	102 (76–143)	102 (75–140)	0.47	1.3
HDL-C	41 (35–48)	43 (36–51)	<0.001	19.4	41 (35–49)	42 (35–49)	0.36	4.5
LDL-C	58 (50–65)	58 (50–64)	0.65	1.1	58 (50–65)	57 (49–64)	0.95	2.0
Statin intensity at study enrollment			0.89	3.4			0.97	3.4
Low	1 (0.3)	14 (0.5)			1 (0.3)	5 (0.5)		
Moderate	354 (99.7)	2,836 (99.5)			338 (99.7)	971 (99.5)		
Follow up LDL-C (mg/dL)*	46 (37–57)	52 (41–62)	<0.001	30.7	46 (38–57)	52 (41–62)	<0.001	26.6

Data are presented as mean ± standard deviation, median (interquartile range), or number (%).
ASCVD = atherosclerotic cardiovascular disease; CAD = coronary artery disease; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; SMD = standard mean difference; TIA = transient ischemic attack.
*Measured at 2–12 months of follow-up (median 8 months).

were treated with moderate-intensity statins. Before the decision to escalate, rosuvastatin 10 mg was the most frequently prescribed regimen in both groups, followed by atorvastatin 10–20 mg. After escalation, atorvastatin 40 mg was most commonly used, followed by rosuvastatin 20 mg (**Supplementary Figure 2**). In the escalation and non-escalation groups, 178 (52.5%) and 485 (49.7%) of the patients, respectively, experienced LLT regimen changes during follow-up. However, all changed regimens belonged to the same intensity categories as before. The median follow-up LDL-C levels at 2–12 months were 46 and 52 mg/dL in the escalation and non-escalation groups, respectively (p<0.001). Low LDL-C levels were partly sustained, and median levels during the entire follow-up period were 56 and 59 mg/dL in the escalation and non-escalation groups, respectively (p<0.001).

Clinical outcomes

At a median follow-up of 5.7 years, 22 and 88 patients in the escalation and non-escalation groups, respectively, experienced MACCE1. The MACCE1 rate was not significantly lower in the escalation group than in the non-escalation group (9.8 and 14.3/1,000 person-years; HR, 0.68; p=0.11) (**Table 2**), and the Kaplan–Meier curves demonstrated similar result (log-rank p=0.108; **Figure 2A**). The most common intervals between LLT escalation and incident MACCE1 were 0–1, 2–3, and 1–2 years, in the order of frequency (**Supplementary Figure 3**). The rate of all-cause death did not differ between the two groups (15.4 and

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Table 2. Incident MACCE and all-cause death in groups with or without LLT escalation

Outcomes	Number of events (/1,000 person-years)		HR (95% CI)	p value
	Escalation (n=339)	Non-escalation (n=976)		
MACCE1	22 (9.8)	88 (14.3)	0.68 (0.43–1.09)	0.11
MACCE2	55 (24.5)	218 (35.4)	0.70 (0.52–0.94)	0.017
Cardiovascular death	6 (2.7)	36 (5.8)	0.45 (0.19–1.06)	0.067
Nonfatal myocardial infarction	4 (1.8)	25 (4.1)	0.44 (0.15–1.27)	0.13
Nonfatal ischemic stroke	13 (5.8)	34 (5.5)	1.07 (0.56–2.04)	0.84
Coronary revascularization	30 (13.4)	132 (21.5)	0.64 (0.43–0.96)	0.029
Peripheral revascularization	9 (4.0)	35 (5.7)	0.74 (0.35–1.54)	0.42
All-cause death	38 (15.4)	144 (20.5)	0.76 (0.53–1.09)	0.14

CI = confidence interval; HR = hazard ratio; LLT = lipid-lowering therapy; MACCE = major cardiovascular and cerebrovascular event.

20.5/1,000 person-years; HR, 0.76; p=0.14) (**Table 2**), as shown in the Kaplan–Meier curves (log-rank p=0.14; **Figure 2B**). Conversely, the MACCE2 rate was significantly lower in the escalation group (24.5 and 35.4/1,000 person-years; HR, 0.70; p=0.017) (**Table 2**), as also shown in the Kaplan-Meier curves (log-rank p=0.016; **Figure 2C**). The coronary revascularization rate was significantly lower in the escalation group than in the non-escalation group (HR, 0.64; p=0.029). The cardiovascular death rate tended to be lower in the escalation

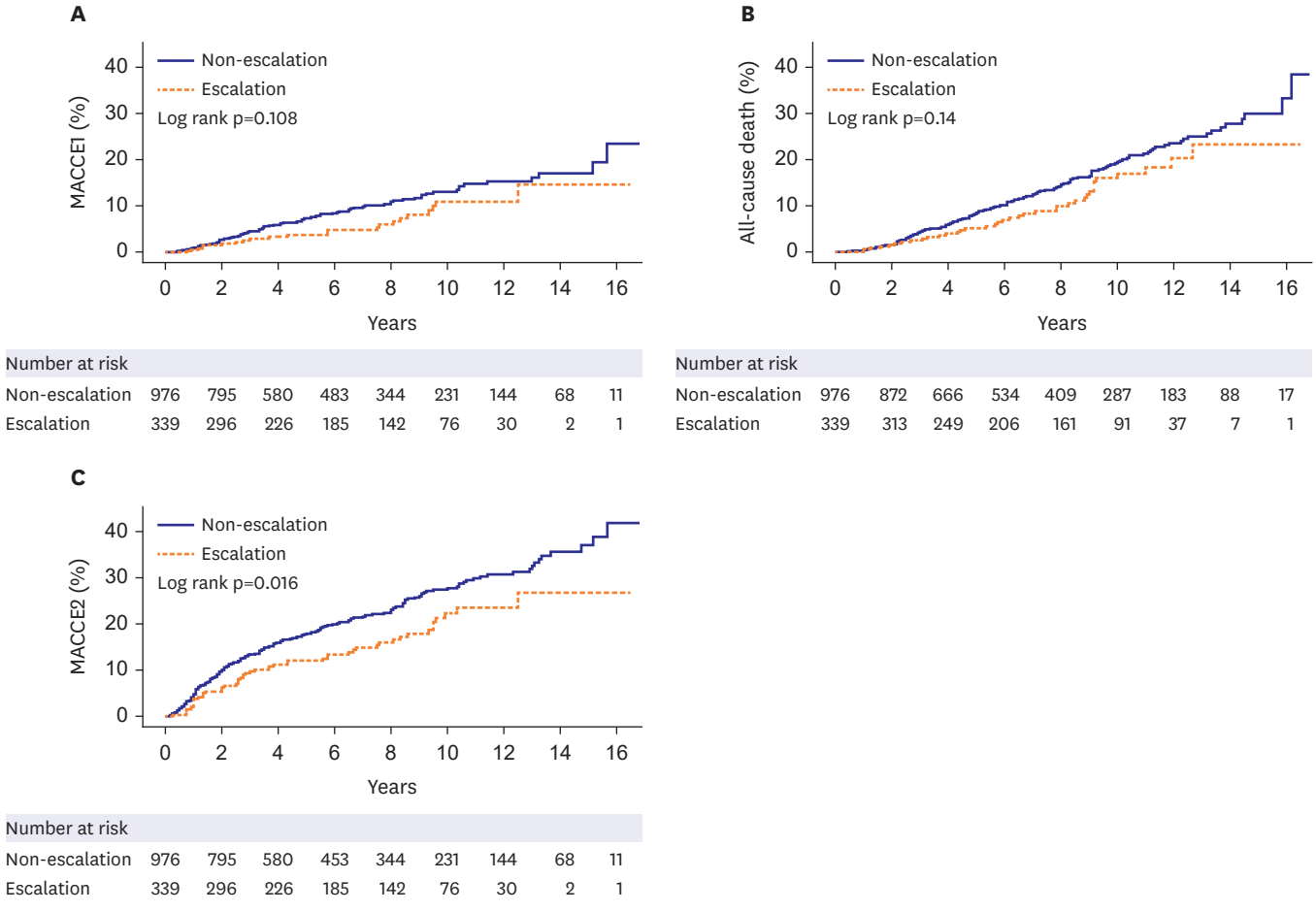

Figure 2. Kaplan–Meier curves. (A) MACCE1, (B) all-cause death, and (C) MACCE2.
MACCE1 is composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal ischemic stroke. MACCE2 is composite of MACCE1 and coronary or peripheral revascularization.
MACCE = major adverse cardiovascular and cerebrovascular events.

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Table 3. Factors associated with MACCE1

Factors	Unadjusted HR (95% CI)	p value	Adjusted HR (95% CI)	p value
Age	1.05 (1.03–1.08)	<0.001	1.04 (1.02–1.06)	<0.001
Male	0.74 (0.49–1.11)	0.15	0.93 (0.58–1.48)	0.75
Hypertension	1.42 (0.97–2.07)	0.071	1.12 (0.75–1.67)	0.57
Diabetes mellitus	1.25 (0.86–1.84)	0.25	1.00 (0.67–1.49)	0.99
Smoking	0.75 (0.48–1.15)	0.19	0.85 (0.53–1.39)	0.53
Chronic kidney disease	3.66 (2.00–6.69)	<0.001	2.57 (1.36–4.87)	0.004
Atrial fibrillation	2.25 (1.35–4.71)	0.004	1.47 (0.72–2.99)	0.29
Heart failure	3.18 (1.69–5.98)	<0.001	1.89 (0.92–3.87)	0.083
Body mass index	0.95 (0.89–1.01)	0.085	0.98 (0.92–1.05)	0.53
Multi-vessel CAD	2.42 (1.46–4.01)	0.001	2.18 (1.30–3.67)	0.003
Triglyceride	1.00 (1.00–1.00)	0.57	1.00 (1.00–1.01)	0.068
HDL-C	0.99 (0.98–1.01)	0.51	1.00 (0.98–1.02)	0.86
LDL-C	0.99 (0.98–1.01)	0.52	1.00 (0.98–1.02)	0.90
LLT escalation	0.68 (0.43–1.09)	0.11	0.70 (0.44–1.13)	0.14

Multivariate analysis was performed using the following variables: age, sex, hypertension, diabetes mellitus, chronic kidney disease, HDL-C and LDL-C levels at study enrollment, and LLT escalation.
CAD = coronary artery disease; CI = confidence interval; HDL-C = high-density lipoprotein cholesterol; HR = hazard ratio; LDL-C = low-density lipoprotein cholesterol; LLT = lipid-lowering therapy; MACCE = major adverse cardiovascular and cerebrovascular events.

group (HR, 0.45; p=0.067). In contrast, the rates of other individual MACCE components did not differ significantly between the two groups (**Table 2**).

In the patient subgroup with coronary artery disease, MACCE1 rate was lower in those with LLT escalation (7.4 and 13.7/1,000 person-years in LLT escalation and non-escalation groups, respectively; HR, 0.53; p=0.027) (**Supplementary Table 1**), and this difference was also observed in the Kaplan-Meier curves (log-rank p=0.025). In contrast, the patient subgroup with ischemic stroke/transient ischemic attack demonstrated that MACCE1 rate did not differ between the two groups (36.2 and 26.2/1,000 person-years in each group, respectively; HR, 1.27; p=0.65) (**Supplementary Table 1**). This finding was also shown in the Kaplan-Meier curves (log-rank p=0.63).

Factors associated with major adverse cardiovascular and cerebrovascular events 1 and subgroup analysis

In the univariate analysis, age, chronic kidney disease, atrial fibrillation, heart failure, and multivessel CAD were significantly associated with incident MACCE1. In the multivariate analysis, age (HR, 1.04; p<0.001), chronic kidney disease (HR, 2.57; p=0.004), and multivessel CAD (HR, 2.18; p=0.003) were positive predictors of MACCE1 (**Table 3**). Subgroup analyses revealed that no factors significantly influenced the relationship between LLT escalation and the risk of MACCE1 (**Figure 3**).

DISCUSSION

In the current study with a median follow-up of 5.7 years, we found that the MACCE1 risk was not significantly lower (HR, 0.68) in patients who received LLT escalation than in those who did not. No significant differences in the risk of all-cause death were observed. However, MACCE2 risk was lower in patients with LLT escalation. In this population with LDL-C levels <70 mg/dL after moderate-intensity statin use, age, chronic kidney disease, and multivessel CAD were additionally identified as predictors of MACCE. The effects of LLT escalation did not differ based on any subgroups of clinical features.

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Subgroups	Escalation	Non-escalation	HR (95% CI)	p for interaction
Age				0.985
≥65	14/169	57/500	0.69 (0.38–1.23)	
<65	8/170	31/476	0.69 (0.32–1.51)	
Sex				0.128
Male	12/256	65/736	0.52 (0.28–0.96)	
Female	10/83	23/240	1.10 (0.52–2.31)	
Hypertension				0.980
Yes	13/171	51/497	0.68 (0.37–1.24)	
No	9/168	37/479	0.68 (0.33–1.42)	
Diabetes mellitus				0.125
Yes	12/123	31/341	1.02 (0.52–1.99)	
No	10/216	57/635	0.49 (0.25–0.96)	
Smoking				0.782
Current smoker	7/127	26/365	0.75 (0.33–1.74)	
Non-smoker	11/166	43/475	0.65 (0.33–1.26)	
Body mass index				0.459
≥25	7/138	35/388	0.54 (0.24–1.21)	
<25	15/201	53/588	0.78 (0.44–1.38)	
Number of diseased vessels				0.904
≥2	12/188	59/529	0.54 (0.29–1.01)	
1	3/108	16/307	0.50 (0.15–1.72)	

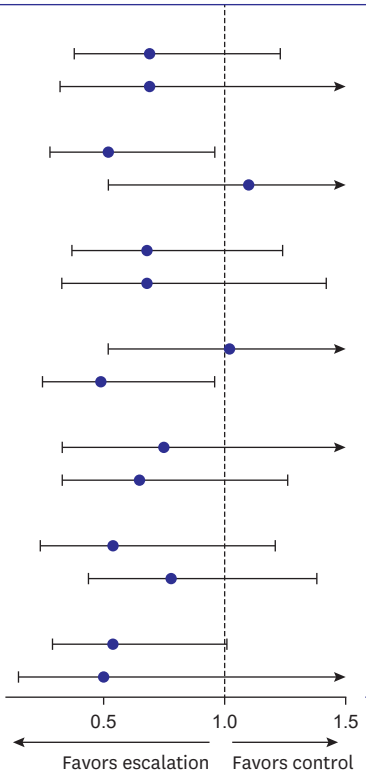

Figure 3. Subgroup analysis of MACCE1.
MACCE1 is composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal ischemic stroke.
CI = confidence interval; HR = hazard ratio; MACCE = major adverse cardiovascular and cerebrovascular event.

When LLT was escalated after statin use in previous studies, the cardiovascular benefits were similar, irrespective of the pre-escalation statin intensity. In addition, the LDL-C levels before LLT escalation did not seem to affect the measured benefits.[8-10] The potential influence of pre-escalation LDL-C levels is commonly analyzed using LDL-C categories, such as quartiles. In some studies, the benefits did not significantly differ between patients with pre-escalation LDL-C levels <80 mg/dL and those with higher levels.[9][10] These results are not concordant to ours, which demonstrated uncertain benefit of LLT escalation in patients with pre-escalation LDL-C levels <70 mg/dL. However, LLT escalation was beneficial with regard to MACCE2, the secondary outcome variable in our study. As some studies include revascularization events in the composite primary outcome variable, caution is required when comparing our results with those of others.[9] This may be another point that contributed to the difference in LLT escalation benefits in our study. Conversely, it may be difficult to interpret LLT escalation benefit on MACCE2, our secondary outcome variable. Since coronary/peripheral revascularization could have been partly driven by the physician's subjective decision, the impact of escalation on this outcome in this retrospective study should be interpreted with caution. In addition, the median LDL-C level before LLT escalation was very low (58 mg/dL) in our study participants.

In our previous study of stable CAD and a mean baseline LDL level of 65 mg/dL, we found that patients taking atorvastatin 20 mg (or similar statins) had better cardiovascular outcomes than those of patients taking atorvastatin 10 mg (or similar statins).[15] These findings indicate

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that a relatively high-intensity statin therapy is more effective, even in patients with very low LDL-C levels. This study compared two statin intensities as the first line regimens. However, the current study evaluated the effect of LLT escalation after checking post-statin LDL-C levels, which is an approach that better represents actual clinical practice. Moreover, we analyzed patients receiving moderate-intensity therapy and LLT escalation, which is different from our previous study.

The reasons to escalate LLT in our study population could not be fully understood. However, the most likely explanation is as follows. Major guidelines on LLT recommend LDL-C reduction of ≥50% plus LDL-C <55 mg/dL (Europe) or LDL-C reduction of >50% plus LDL-C <55 or 70 mg/dL (US) as the LDL-C target for patients with ASCVD. Thus, some physicians may have escalated LLT to achieve LDL-C reduction >50% that was not attained by moderate-intensity statins. Conversely, some might have escalated to meet the more aggressive European LDL-C target of <55 mg/dL. In the escalation group, mean LDL-C levels changed from 58 to 46 mg/dL, representing a 20% further reduction in LDL-C. Statin dose doubling is known to lower LDL-C by an additional 6%. However, the additional 6% is calculated from the LDL-C levels before statin therapy.[16] Therefore, when the additional percentage reduction is calculated from the "LDL-C level before doubling" instead of the "LDL-C level before statin," it could be greater than 6%. In addition, some escalated regimens in our study population might have been higher than dose doubling, as shown in **Supplementary Figure 2**. These factors can plausibly explain the 20% further LDL-C reduction observed in our escalation group.

Our study has some potential limitations. Due to the study design and insufficient statistical power, our main result is not appropriate to be interpreted as "equivalent or non-inferior." Furthermore, if confidence interval is considered, the risk of cardiovascular death may be interpreted as close to a decline. Therefore, further studies using larger number of patients would be helpful to obtain more solid conclusion. As the current study had a retrospective design, the 2 study groups (LLT escalation and non-escalation) may have had slightly different characteristics even after propensity score matching. However, we matched all possible variables and comorbidities to achieve a well-balanced population. In addition, we excluded patients with missing laboratory values or records, which may have caused a potential bias. This is an inevitable limitation of studies with similar designs. In addition, approximately 85% of the study subjects were enrolled as they had CAD, making coronary revascularization a significant factor in the clinical outcomes. This is a limitation when interpreting the results for patients with stroke. The additive LDL-C reduction from LLT escalation was only partially sustained during the entire follow-up period. The underlying reason for this is not clear from our current data. However, we cannot rule out the possibility that LLT escalation might have resulted in greater and significant benefits for our primary outcome, if the additive LDL-C reduction could have been sustained longer. In addition, patients in the escalation group who had discontinued or reduced LLT intensity were excluded from our study. Therefore, those who experienced clinical events in the escalation group might be underestimated. Although the impact of this bias is not clear, it is still another limitation of the current study. Nonetheless, we analyzed the East Asian population, which has been relatively neglected in many landmark studies on LLT. Therefore, demonstrating the effect of intensive LLT in East Asian patients with ASCVD was noteworthy.

In conclusion, LLT escalation did not reduce hard cardiovascular outcomes and call-cause death in patients with ASCVD who achieved LDL-C levels <70 mg/dL after the use of moderate-intensity statins. However, it reduced revascularization rates in this population.

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SUPPLEMENTARY MATERIALS

Supplementary Table 1

Incidence of MACCE1 in patients with coronary artery disease and ischemic stroke/transient ischemic attack

Supplementary Figure 1

Distribution of propensity score before (A) and after (B) matching. C-indices for MACCE1 were 0.681 and 0.703 in unmatched and matched populations, respectively.

Supplementary Figure 2

Lipid-lowering regimens used in each group.

Supplementary Figure 3

Intervals between LLT escalation and MACCE1.

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