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The low-density lipoprotein cholesterol lowering is an ineffective surrogate marker of statin responsiveness to predict cardiovascular outcomes

The 10-year experience of matched population (a STROBE-compliant article)

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Abstract

Statins therapy decrease both low-density lipoprotein cholesterol (LDL-C) levels and the risk of atherosclerotic cardiovascular disease (ASCVD) with considerable individual variability. Whether the amount of LDL-C lowering is a surrogate maker of statin responsiveness to ASCVD prevention has not been fully investigated. Among 2352 eligible patients with statin prescriptions in a cardiovascular center between January 2005 and February 2014, one-third of patients (33%) on statin therapy failed to achieve effective reductions in LDL-C (LDL-C level reduction of less than 15%). By using, propensity-score matched population (480 pairs, n = 960), the 5-year cumulative incidences of total major adverse cardiac events (MACE) were evaluated. The 5-year total MACE did not differ between normal cholesterol responders and non-responders (15.4% vs 16.1%, respectively; $P = .860$). In the subgroup analysis, male sex, older age, percutaneous coronary intervention, and heart failure were positive predictors, and dyslipidemia at the beginning of statin therapy was the only negative predictor of MACE in the 5-year follow-up (all P value $< .05$). However, cholesterol responsiveness after statin therapy did not influence the incidence of MACE ($P = .860$). The amount of LDL-C lowering did not predict beneficial effect on clinical outcomes of ASCVD after statin therapy. This result supports that given statin therapy, total ASCVD risk reduction should be tailored, which may not dependent to adherence to degree of LDL-C lowering or LDL-C goal based treatment.

Abbreviations: ACC = American College of Cardiology, ACE = angiotensin I-converting enzyme, AHA = American Heart Association, Apo = apolipoprotein, APOE = apolipoprotein E, ASCVD = atherosclerotic cardiovascular disease, CAG = coronary angiography, CTTC = Cholesterol Treatment Trialists' Collaboration, EAS = European Atherosclerosis Society, ESC = European Society of Cardiology, HbA1c = glycated hemoglobin A1c, HDL-C = high-density lipoprotein cholesterol, HMG-CoA = 3-hydroxy-3-methylglutaryl coenzyme A, HMGCR = 3-hydroxy-3-methylglutaryl-CoA reductase, hsCRP = high-sensitivity C-reactive protein, LDL-C = low-density lipoprotein cholesterol, LDLR = low-density lipoprotein receptor, MACE = major advanced cardiovascular

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event, NPC1L1 = Niemann-Pick C1-Like 1, PCI = percutaneous coronary intervention, PCSK9 = proprotein convertase subtilisin/kexin type 9, PTCA = percutaneous transluminal coronary angioplasty, RCT = randomized controlled trial, Total-C = total cholesterol, VLDL-C = very-low-density lipoprotein cholesterol.

Keywords: coronary artery disease, disease progression, low-density lipoprotein cholesterol, statin responsiveness

1. Introduction

Atherosclerotic cardiovascular disease (ASCVD) is the most important mortality contributor worldwide.[1,2] Macrophages are the main inflammatory cells that transform into foam cells through the ingestion of cholesterol in atherosclerotic plaques.[3,4] Statins are the most popular medications used for the prevention of acute cardiac events in clinical practice.[5,6] They reduce both low-density lipoprotein cholesterol (LDL-C) levels by inhibiting 3-hydroxy-3-methylglutaryl coenzyme A reductase, and high-sensitivity C-reactive protein (hsCRP) levels by pleiotropic effects.[5] Previous studies reported that statin therapy is associated with decreased atherosclerotic volume in addition to a far more reduced plaque rupture rate.[7–9]

Two main guidelines for the management of dyslipidemia are implemented in clinical practice. Despite their similar purposes, however, both consensus opinions have not been fully tested. While 1 recommends target levels of LDL-C with statin therapy and the other does not support this recommendation. The European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) guidelines set fixed treatment targets for LDL-C levels, primarily based on the results of a meta-analysis of several clinical trials (Cholesterol Treatment Trialists' Collaboration [CTTC]) that involved 170,000 patients and showed a cholesterol lowering-dependent ASCVD risk reduction.[10–12] The overall ESC/EAS guideline strongly recommends modulating the intensity of statin therapy, according to the total cardiovascular risk, in order to achieve a target LDL-C level.[12]

However, the American College of Cardiology (ACC)/American Heart Association (AHA) guidelines do not recommend a treat-to-goal strategy for achieving a target LDL-C level, which has been widely accepted.[13] Expert panel members reported that the evidence from clinical trials on statin therapy clearly showed that ASCVD events are reduced by using the maximum tolerated statin intensity in groups shown to benefit from the therapy. However, no randomized controlled trials (RCT) have been conducted that titrated drug therapy to specific LDL-C goals to improve ASCVD outcomes.[13] Therefore, this guideline did not suggest testing for serum LDL-C levels in order to confirm the effectiveness of statins. As a result, many clinicians express concern when prescribing statins for the prevention of cardiovascular disease because patient response to cholesterol-lowering therapy with hypolipidemic agents showed considerable individual variation. A recent study reported that 20% of patients treated with statin therapy exhibited refractoriness and showed greater atheroma progression and less regression.[14] In addition, only few studies assessed the relationship between the amount of LDL-C lowering and clinical cardiovascular outcomes after statin therapy.

In this study, we hypothesized that the LDL-C level is not representative of cholesterol burden and inflammatory status in atherosclerosis, especially after statin therapy. Given the same intensity of statins, the continuous nature of the relationship between LDL-C and total ASCVD risk may became altered. Therefore, we aimed to investigate the impacts of LDL-C lowering levels on clinical ASCVD outcomes among normal cholesterol responders and non-responders after statin therapy, based on the 10-year experience of a matched cohort.

2. Materials and methods

2.1. Study population, definition of risk factors, and clinical follow-up

Between January 2005 and February 2014, 29,175 consecutive statin-naive patients visited the Cardiovascular Center at the Korea University Guro Hospital in Seoul, South Korea. The institutional review board of Guro Hospital, Korea University (#KUGH15095) approved this study. Among these patients, 2352 with available data on both baseline blood lipid and hsCRP values, which were measured after 6 to 9 months of statin therapy, constituted the study population. These subjects received statin treatment (atorvastatin, simvastatin, rosuvastatin, pitavastatin, or fluvastatin) for at least 6 months after baseline lipid profile testing and were followed up clinically for at least 5 years. We defined cholesterol non-responder to statin therapy as a reduction in LDL-C level by less than 15%. On the other hands, cholesterol responder to statin was defined as more than 15% reduction in LDL-C level.[14] Demographic data and risk factors such as the presence of a previous myocardial infarction, coronary spasm, heart failure, peripheral arterial disease, chronic kidney disease, and stroke, as well as medications, were also evaluated. Hypertension was defined as a systolic blood pressure of ≥140 mm Hg and/or a diastolic blood pressure of ≥90 mm Hg on at least 2 consecutive readings in the outpatient clinic. Diabetes was defined as a fasting blood glucose level ≥126 mg/dl, a glycated hemoglobin A1c (HbA1c) level >6.5%, or current use of medications. The serum lipid profile, including LDL-C, high-density lipoprotein cholesterol (HDL-C), and triglyceride, fasting glucose, and serum hsCRP levels were measured by using chemiluminescence (Immulite; DPC Cirrus Inc., Los Angeles, CA, USA). Apolipoprotein (Apo) A-1, Apo B, Apo C-II, and Apo E levels were measured using the immunoturbidimetric assay (Sekisui Medical Co., Ltd, Tokyo, Japan). High-, moderate-, and low-intensity statin therapies were defined according to the 2018 ACC/AHA guidelines on the treatment of blood cholesterol at any time during the study.[13] The LDL-C and hsCRP values taken at baseline and after 6 to 9 months of treatment with statin therapy were recorded. The demographic data, cardiovascular risk factors, and medical history records were mainly dependent on patient self-reporting, but the final records were left to physician discretion after all of the subjects had comprehensive evaluation of self-reported data and in-hospital examination results. Total major adverse cardiac events (MACEs) included total death, nonfatal myocardial infarction (MI), fatal MI, nonfatal stroke, and percutaneous coronary intervention (PCI). The cumulative 5-year incidences of MACE, acute MI, PCI, and total death were compared between the groups.

2.2. Statistical analysis for the laboratory and clinical data

For continuous variables, differences between 2 groups were evaluated by using the Student *t* test or Mann–Whitney rank sum test, and those between the 3 groups were evaluated by using the one-way analysis of variance test. Data were expressed as mean ± standard deviation. For discrete variables, differences were expressed as counts and percentages and analyzed by using either the χ^2 or Fisher exact test, when appropriate. In order to adjust for potential confounders, a propensity score matching (PSM) analysis was performed using the logistic regression model. We tested all available variables that could be of potential relevance, including age, sex, cardiovascular disease, cardiovascular risk factors (hypertension, diabetes, dyslipidemia, heart failure, chronic kidney disease, coronary artery disease, atrial fibrillation, and cerebrovascular accident), statin therapy (duration of treatment, intensity, and calendar date of treatment), current medications (antihypertensive agents, including angiotensin II receptor blockers, angiotensin-converting enzyme inhibitors, calcium channel blockers, beta blockers, and diuretics; anti-diabetic medication and insulin; and aspirin), and basal laboratory values before statin therapy (total cholesterol, LDL-C, HDL-C, triglyceride, and hsCRP levels). A two-tailed *P* value of $<.05$ was considered to be statistically significant. The incidence of MACEs at 5-year follow-up was estimated by using the Kaplan–Meier method, and between-group differences were compared using the log-rank test. The prognostic factors of the total MACEs were assessed using multivariate Cox proportional hazard regression models. All statistical analyses were performed using the SPSS 20.0 (SPSS Inc., Chicago, IL, USA) statistical software.

3. Results

3.1. Clinical characteristics, risk factors, medications, and laboratory findings of the entire study population

We enrolled 2352 eligible patients for statin therapy, of whom 66.6% were responders and 33.3% were non-responders to statin therapy (n = 1569 vs n = 783). The baseline clinical characteristics of the statin responders and non-responders are described in Table 1. In the entire population, the non-responders were more likely to have a history of dyslipidemia, elevated LDL-C levels, and hypertriglyceridemia, and less likely to have impaired glucose tolerance or atrial fibrillation. However, no significant differences in other underlying cardiovascular diseases and risk factors were found between the responders and non-responders (Table 1). The patients' histories of statin usage showed that the non-responders had longer duration of statin use than the responders (1480 ± 798 days vs 1571 ± 812 days; $P = .009$). Statin non-responders were less likely to receive moderate- to high-intensity statin treatment (30.4% vs 25.4%; $P = .011$) and more likely to receive moderate-intensity treatment (53.6% vs 59.2%; $P = .009$). Most of the patients in both groups received atorvastatin, simvastatin, or rosuvastatin, with no statistical differences. However, in the rest of the population, the statin non-responders used pitavastatin (9.8% vs 12.7%; $P = .029$) and fluvastatin (6.5% vs 3.8%; $P = .007$) more and less frequently, respectively. Although statin non-responders used calcium channel and diuretics more frequently, the use of other anti-atherosclerotic medical therapies at follow-up was similar between the 2 groups (Supplementary Table S1, http://links.lww.com/MD/D502).

The biochemical laboratory parameters at baseline and follow-up are summarized in Supplementary Table S2, http://links.lww.com/MD/D503. Baseline laboratory findings did not differ between the 2 groups, except for cholesterol and apolipoprotein levels. The non-responders had lower levels of LDL-C and Apo B, and higher levels of HDL-C, Apo A-1, and Apo E compared to the responders. At follow-up, the non-responders had significantly higher LDL-C levels. In particular, the non-responders showed a 12.8% decrease in LDL-C levels at follow-up, with higher levels of triglycerides, HDL-C, Apo B, Apo C-II, Apo A-I, Apo E, fasting glucose, and HbA1c than at baseline. Although they had higher hsCRP levels, the differences were not statistically significant ($P = .184$).

3.2. Clinical characteristics of the propensity score-matched population

In order to adjust for potential confounders, a PSM analysis was performed using a logistic regression model (480 pairs, n = 960, c-statistic = 0.842). After PSM analysis, the baseline characteristics, medication history, and biochemical values in the 2 groups were well balanced (Table 1, and Supplementary Table S1, http://links.lww.com/MD/D502, 3, http://links.lww.com/MD/D504). However, all of the lipid profiles, including apolipoprotein levels during follow-up, were higher in the non-responders compared to the responders, except for the hsCRP levels. The statin non-responders showed a 7.3% decrease in LDL-C levels. Patient responses to statin therapy, based on changes in LDL-C and hsCRP levels, are shown in Figure 1. Individual variations in cholesterol reduction rate showed that the median LDL-C level reduction after statin therapy was 40.2% (interquartile range [IQR]: 29.7%–50.0%) in the statin responders and 5.7% (IQR: −25.3% to 5.1%) in the non-responders while the median hsCRP level reduction rate after statin therapy was 35.1% (IQR: −41.0% to 73.8%) in the responders and 15.6% (IQR: −75.3% to 65.5%) in the non-responders.

3.3. Comparison of clinical outcomes between the statin responders and non-responders in the matched population

The clinical follow-up durations for the matched population of non-responders and responders were similar ($P = .991$; Supplementary Table S3, http://links.lww.com/MD/D504). The 5-year incidence of MACEs did not significantly differ between the responders and non-responders despite the different levels of LDL-C concentrations that were achieved after statin therapy in the matched population (16.1% vs 15.4%; $P = .860$; Fig. 2a). In addition, the acute myocardial infarction (AMI), percutaneous coronary intervention (PCI), and total death rates during the 5-year follow-up did not significantly differ between the 2 groups ($P = .648$,.274, and.995, respectively; Fig. 2b-2d). The subgroup analysis of the adjusted hazard ratios for 5-year incidence in the matched populations showed that the presence of risk factors or ASCVD after statin therapy had no significant effect on the clinical outcomes of total mortality, cardiac death, non-fatal MI, non-fatal stroke, and PCI (Fig. 3).

The multivariate analysis of the prognostic factors for total MACEs during the 5-year follow-up after statin therapy in the propensity-matched patients revealed that male sex, older age, the presence of atherothrombotic disease requiring PCI, and heart failure were positive predictors, and that dyslipidemia at the

Table 1

Baseline clinical characteristics and statin usage of the total and propensity score-matched populations.

	Total patients			Matched patients		
Variables	**Responder (n = 1569)**	**Non-responder (n = 783)**	***P* value**	**Responder (n = 480)**	**Non-responder (n = 480)**	***P* value**
Male	822 (52.3)	380 (48.5)	.078	248 (51.6)	230 (47.9)	.245
Age	59 ± 11	59 ± 10	.603	59 ± 10	59 ± 11	.526
BMI	24.7 ± 3.2	24.6 ± 3.0	.726	24.4 ± 3.0	24.8 ± 2.9	.152
HTN	1,138 (72.5)	587 (74.9)	.208	343 (71.4)	346 (72.0)	.830
DM	575 (36.6)	286 (36.5)	.954	180 (37.5)	177 (36.8)	.841
IGT[†]	613 (39.0)	252 (32.1)	.001	188 (39.1)	180 (37.5)	.595
Dyslipidemia[‡]	1,020 (65.0)	674 (86.0)	<.001	377 (78.5)	386 (80.4)	.472
Hyperlipidemia (Total-C)[a]	557 (35.5)	483 (61.6)	<.001	247 (51.4)	276 (57.5)	.060
Hyperlipidemia (LDL-C)[b]	787 (50.1)	557 (71.1)	<.001	304 (63.3)	318 (66.2)	.344
Hypertriglyceridemia[c]	630 (40.1)	395 (50.4)	<.001	227 (47.2)	224 (46.6)	.846
Low HDL-C[d]	300 (19.1)	146 (18.6)	.782	99 (20.6)	85 (17.7)	.251
PCI	328 (20.9)	143 (18.2)	.131	95 (19.7)	83 (17.2)	.319
History	21 (1.3)	9 (1.1)	.700	6 (1.2)	4 (0.8)	.525
Onset[§]	308 (19.6)	134 (17.1)	.141	89 (18.5)	79 (16.4)	.396
CAS	92 (5.8)	49 (6.2)	.704	31 (6.4)	30 (6.2)	.895
History	30 (1.9)	13 (1.6)	.668	12 (2.5)	7 (1.4)	.247
Onset[§]	62 (3.9)	36 (4.5)	.460	19 (3.9)	23 (4.7)	.528
Arrhythmia	79 (5.0)	23 (2.9)	.019	14 (2.9)	15 (3.1)	.850
History	48 (3.0)	15 (1.9)	.106	9 (1.8)	12 (2.5)	.508
Onset[§]	62 (3.9)	36 (4.5)	.460	19 (3.9)	23 (4.7)	.528
Chest pain requiring CAG	158 (10.0)	92 (11.7)	.213	49 (10.2)	50 (10.4)	.915
History	75 (4.7)	46 (5.8)	.257	25 (5.2)	20 (4.1)	.445
Onset[§]	83 (5.2)	46 (5.8)	.557	24 (5.0)	30 (6.2)	.401
Heart failure	172 (10.9)	80 (10.2)	.582	47 (9.7)	47 (9.7)	ns
Renal dysfunction	68 (4.3)	33 (4.2)	.893	23 (4.7)	23 (4.7)	ns
Thyroid disease	152 (9.6)	91 (11.6)	.146	49 (10.2)	49 (10.2)	ns
Statin duration (days)	1480 ± 798	1,571 ± 812	.009	1,541 ± 778	1,535 ± 844	.907
Statin Intensity[¶]			.029			.676
High	44 (2.8)	27 (3.4)	.390	16 (3.3)	12 (2.5)	.443
High-moderate	478 (30.4)	199 (25.4)	.011	142 (29.5)	130 (27.0)	.390
Moderate	841 (53.6)	464 (59.2)	.009	261 (54.3)	276 (57.5)	.329
Low	206 (13.1)	93 (11.8)	.390	61 (12.7)	62 (12.9)	.923
Type of Statin						
Atorvastatin	526 (33.5)	266 (33.9)	.829	173 (36.0)	156 (32.5)	.248
Simvastatin	418 (26.6)	211 (26.9)	.874	107 (22.2)	132 (27.5)	.062
Rosuvastatin	277 (17.6)	115 (14.6)	.069	91 (18.9)	68 (14.1)	.046
Pitavastatin	154 (9.8)	100 (12.7)	.029	53 (11.0)	62 (12.9)	.371
Pravastatin	128 (8.1)	66 (8.4)	.822	45 (9.3)	41 (8.5)	.651
Fluvastatin	103 (6.5)	30 (3.8)	.007	30 (6.2)	23 (4.7)	.323
Lovastatin	1 (0.0)	1 (0.1)	.555	0 (0.0)	1 (0.2)	ns

[†] According to the National Cholesterol Education Program guidelines.
[‡] Impaired glucose tolerance (HbA1c level > 5.7%).
[§] Referred to a cardiovascular center at the period of initial statin therapy.
[¶] According to ACC/AHA guidelines (Supplementary Table 4).
[a] Hyperlipidemia (Total-C level > 5.17 mmol/L).
[b] hyperlipidemia (LDL level > 3.36 mmol/L).
[c] hypertriglyceridemia (triglyceride level > 1.69 mmol/L).
[d] low HDL (HDL level: male, <0.91 mmol/L; female, <1.03 mg/L).
BMI = body mass index (calculated as weight in kilograms divided by the square of the height in meters.), CAG = coronary angiography, CAS = coronary artery spasm, DM = diabetes mellitus, HDL-C = high-density lipoprotein cholesterol, HTN = hypertension, IGT = impaired glucose tolerance, LDL-C = low-density lipoprotein cholesterol, PCI = percutaneous coronary intervention, Total-C = total cholesterol.

beginning of statin therapy was the only negative predictor of total MACE. However, cholesterol responsiveness or hsCRP levels after statin therapy did not influence the occurrence of MACEs. Hypertension, diabetes, baseline LDL-C level, and hsCRP levels after statin therapy were not significantly predictive of MACE (Table 2).

4. Discussion

In the present study, statin reduced the mean LDL-C level with a wide range of inter-individual variation. The clinical outcomes of ASCVD with statin therapy in both the normal responder and non-responder groups did not significantly different. Given statin therapy, the degree of LDL-C lowering may not be related to the risk reduction of clinical outcomes. Therefore, the LDL-C lowering effects could not be a surrogate marker for statins responsiveness and future clinical outcome.

The concept that "the lower is the better" for LDL-C levels has been widely accepted among the general population who have not been treated with statins. The recent ESC/EAS guidelines still recommend achieving target LDL-C levels based on the results of a meta-analysis reported by the CTTC group,[10,12] which

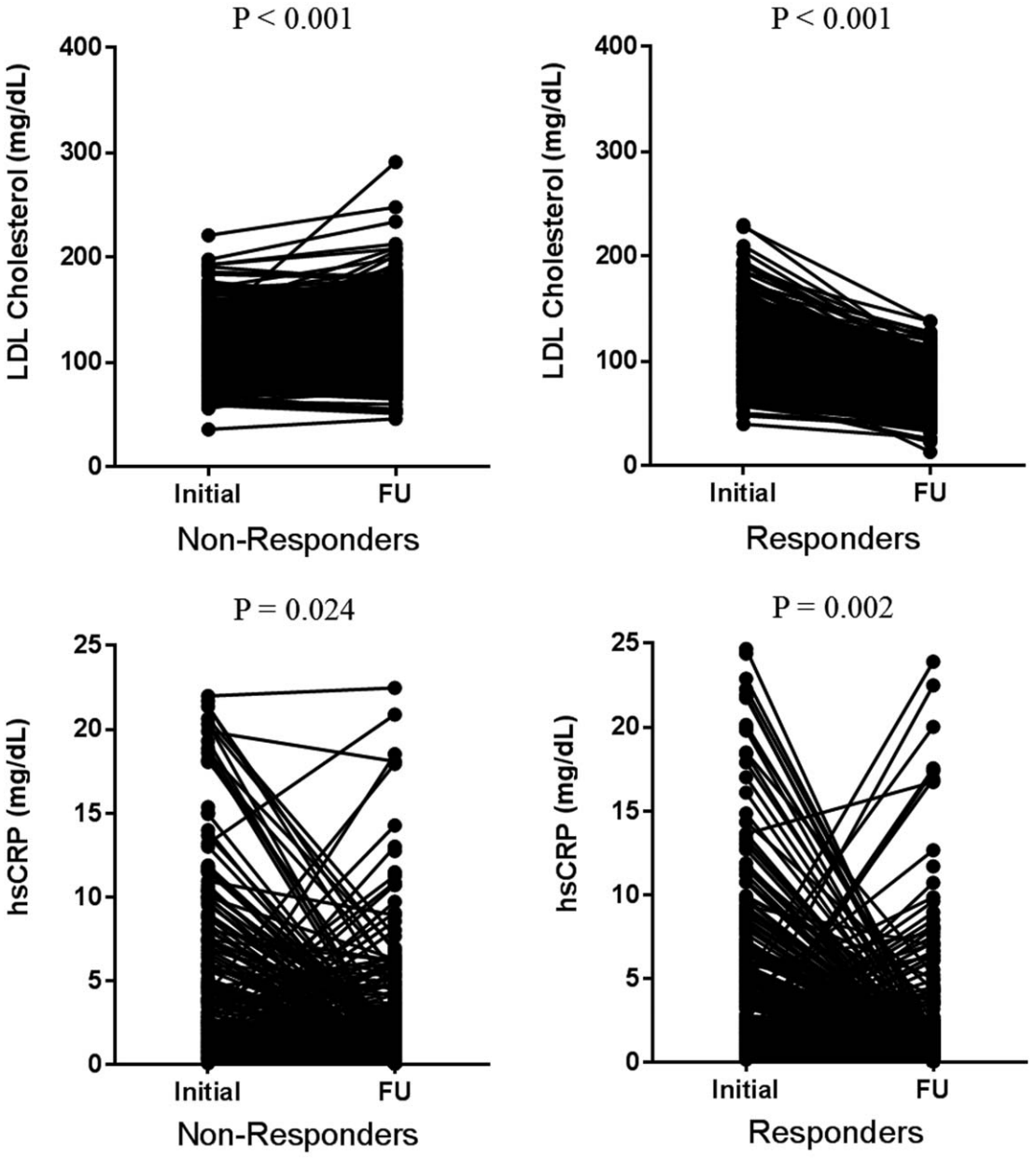


Figure 1. Individual changes in LDL-C and hsCRP levels after statin therapy in the propensity score-matched patients. At follow up, the median reduction rate (%) in LDL-C level was 40.2% (interquartile range [IQR]: 29.7%–50.0%) in the statin responders and 5.7% (IQR: −25.3% to 5.1%) in the statin non-responders. The median reduction rate (%) in hsCRP level was 35.1% (IQR: -−41.0% to 73.8%) in the responders and 15.6% (IQR: −75.3% to 65.5%) in the non-responders. Initial, baseline value before statin therapy; FU, follow-up value after 6–9 months of statin therapy; Non-responders, individuals having an LDL-C reduction of less than 15%; Responders, individuals having an LDL-C reduction of more than 15%; LDL-C, low-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein.

reported that each 1.0 mmol/L reduction in LDL-C with statin therapy is associated with a corresponding 22% reduction in mortality and morbidity from ASCVD.[10] This result applies the same concept of lowering LDL-C levels for the prevention of ASCVD in patients undergoing statin therapy. However, the association between the amount of LDL-C level lowering and the prediction of future cardiovascular outcomes after statin therapy remains to be elucidated.

In the present study, we found that the amount of LDL-C lowering does not predict the clinical outcomes of ASCVD. The benefits of ASCVD risk reduction after statin therapy may not related to LDL-C lowering or LDL-C goal based treatment. This was determined by comparing normal cholesterol lowering responders to non-responders to statin therapy, after adjustment of statin intensity. This result supports the ACC/AHA guidelines,[13] which do not consider target levels of LDL-C for the prevention of ASCVD with statin therapy.[13] Instead, it recommends the modulation of the intensity of statin therapy based on the average expected LDL-C response to a specific statin brand and dose.[13] Two main factors associated with cholesterol metabolism after statin therapy can explain the result of the present study.

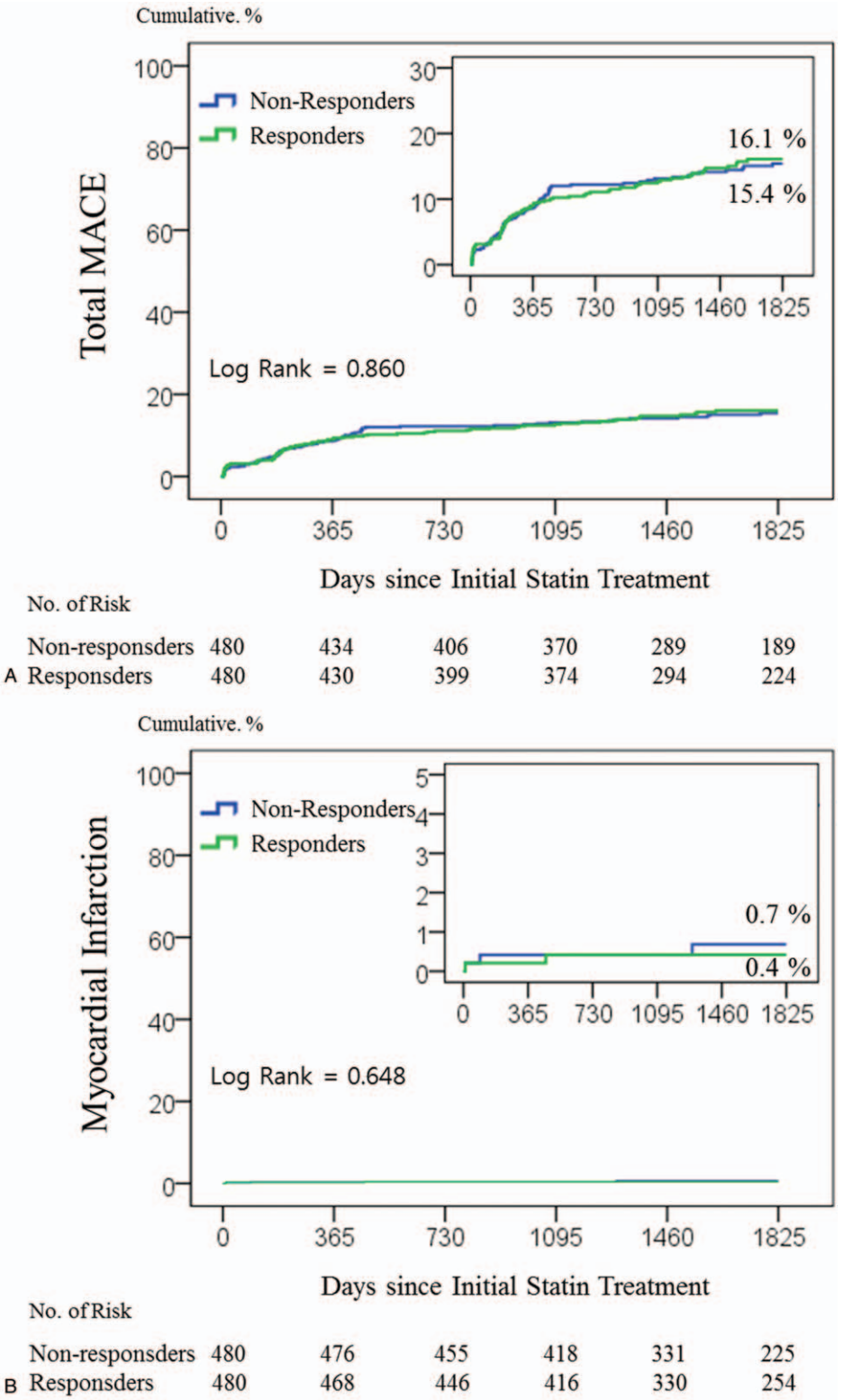


Figure 2. Adjusted cumulative incidences of (A) total MACE, (B) AMI, (C) PCI, and (D) total mortality at the 5-year follow-up of the propensity score-matched patients. AMI = acute myocardial infarction, MACE = major adverse cardiovascular event, PCI = percutaneous coronary intervention; Non-responders, individuals having an LDL-C reduction of less than 15%; Responders, individuals having an LDL-C reduction of more than 15%.

First, cholesterol-lowering responsiveness to statin therapy itself, which is conventionally defined based on the absolute LDL-C level reduction, should be considered as largely dependent on both individual variation and statin intensity.[15,16] The individual variation after statin therapy may be due to the interaction of environmental and genetic factors that affect drug bioavailability, receptor function, or ligand structure.[16] Candidate gene analyses have found variants in known regulators of cholesterol

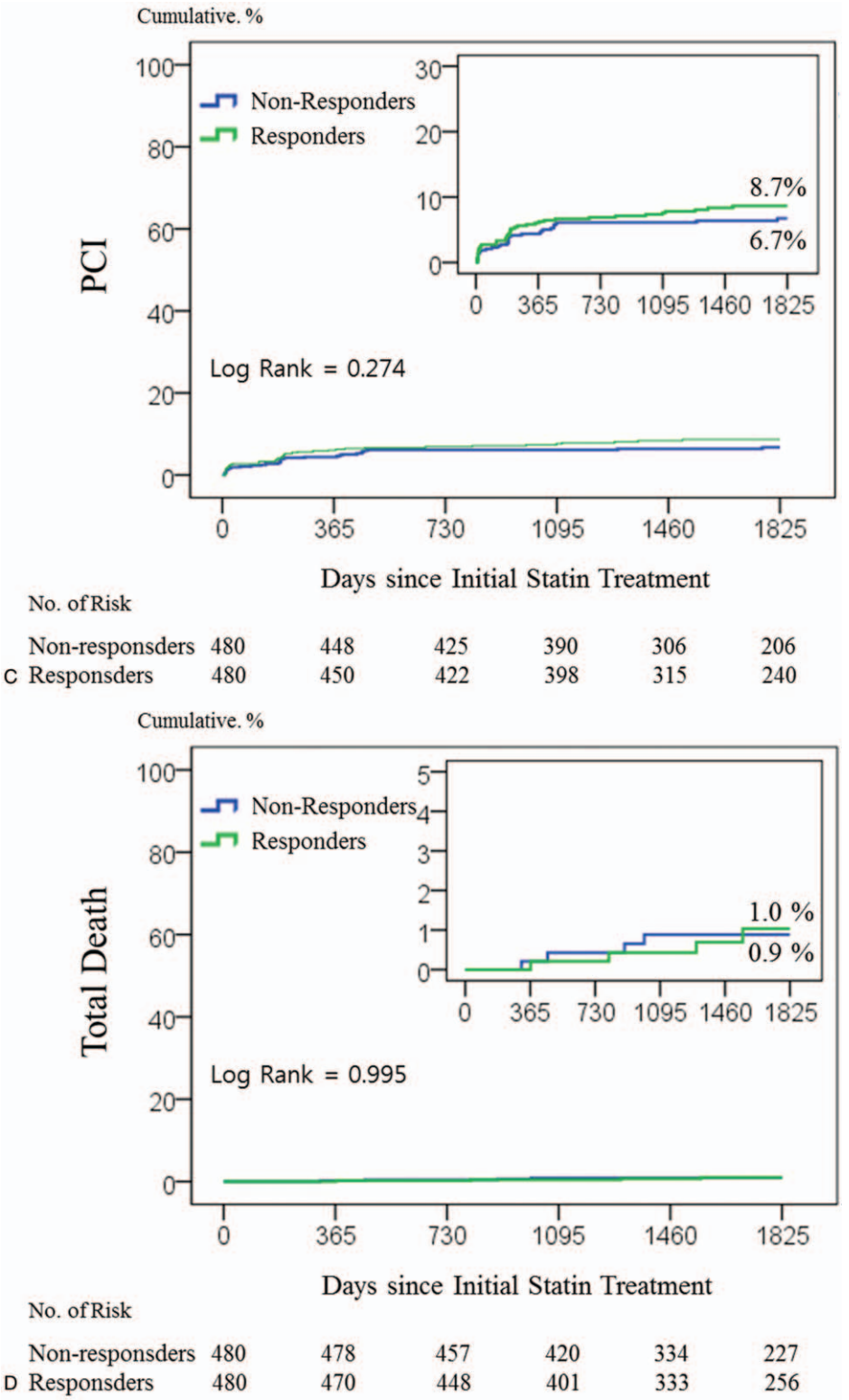


Figure 2. (Continued).

metabolism, such as HMGCR, APOE, PCSK9, ACE, NPC1L1, and LDLR.[17,18] In this study, one third of the study population were non-responders to the cholesterol-lowering effects of statin treatment, which is slightly higher than that reported in a study of Caucasians that accounted for differences in gene expression between different ethnicities.[14] However, comparable effects on clinical outcomes were demonstrated, regardless of the amount LDL-C level lowering from statin therapy. Therefore, the amount of LDL-C reduction by statin therapy is not always a surrogate maker of statin responsiveness to ASCVD prevention. One

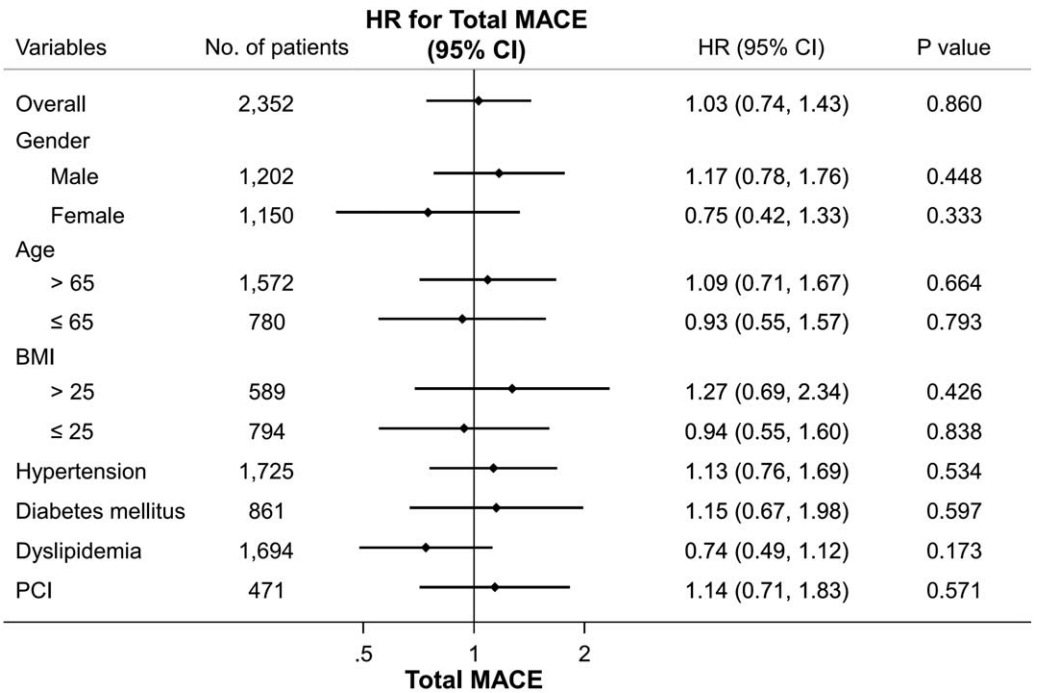


Figure 3. Subgroup analysis of the adjusted hazard ratios for the 5-year incidence of MACE after statin therapy in the propensity score-matched population. MACE = major adverse cardiovascular event, NCEP = national cholesterol education program; Non-responders, individuals having an LDL-C reduction of less than 15%; Responders, individuals having an LDL-C reduction of more than 15%.

plausible explanation for this result is that statins have additional unique pleiotropic effects. Statins improve endothelial and progenitor cell function, increase vascular nitric oxide bioavailability, and reduce oxidative stress.[5,19] In this context, another important issue in the interpretation of the results of statin therapy is related to the concept of statin intensity, which related not only to the amount of LDL-C lowering, but also the degree of pleiotropic effects. A lot of previous clinical trials, including the PROVE IT-TIMI 22, the IDEAL, and the TNT studies, demonstrated a relationship between the amount of LDL-C lowering after statin therapy and the risk of recurrent myocardial infarction or death from coronary causes.[20] Despite the fact that these studies consistently demonstrated that lower cholesterol levels resulted in better outcomes, it seems difficult to conclude that the amount of LDL-C lowering has a critical role in ASCVD prevention because of the mixed statin intensities affecting the amount of LDL-C in those studies. Therefore, when evaluating the relationship between LDL-C levels and ASCVD outcomes in statin trials, statin intensity should be carefully adjusted and stratified, in order to avoid the interference of the effect of statin intensity on lowering the LDL-C levels. The same issue can also be encountered in the CTTC meta-analysis that reported the relationship between the amount of LDL-C level lowering and primary outcome without adjustment of statin intensity.[10]

Table 2

Multivariate analysis of prognostic factors of total MACE over 5 years of follow-up in the propensity score-matched patients.

Variables	HR (95% CI)	*P* value
Statin responder	1.03 (0.74–1.43)	.860
Male	2.05 (1.44–2.90)	<.001
Age	1.01 (1.00–1.03)	.030
BMI	0.97 (0.90–1.03)	.393
HTN	0.82 (0.57–1.16)	.271
DM	0.97 (0.69–1.37)	.906
Dyslipidemia*	0.43 (0.30–0.61)	<.001
PCI	5.29 (3.81–7.36)	<.001
Atrial fibrillation	0.22 (0.03–1.59)	.135
Heart failure	1.80 (1.14–2.83)	.011
Renal dysfunction	0.67 (0.24–1.81)	.435
Thyroid disease	1.31 (0.80–2.15)	.281
Baseline LDL-C	1.00 (0.99–1.00)	.187
Follow-up LDL-C	1.00 (0.99–1.00)	.942
Baseline hsCRP	1.00 (0.99–1.01)	.083
Follow-up hsCRP	1.01 (0.99–1.02)	.163

* According to the National Cholesterol Education Program guideline.[28]

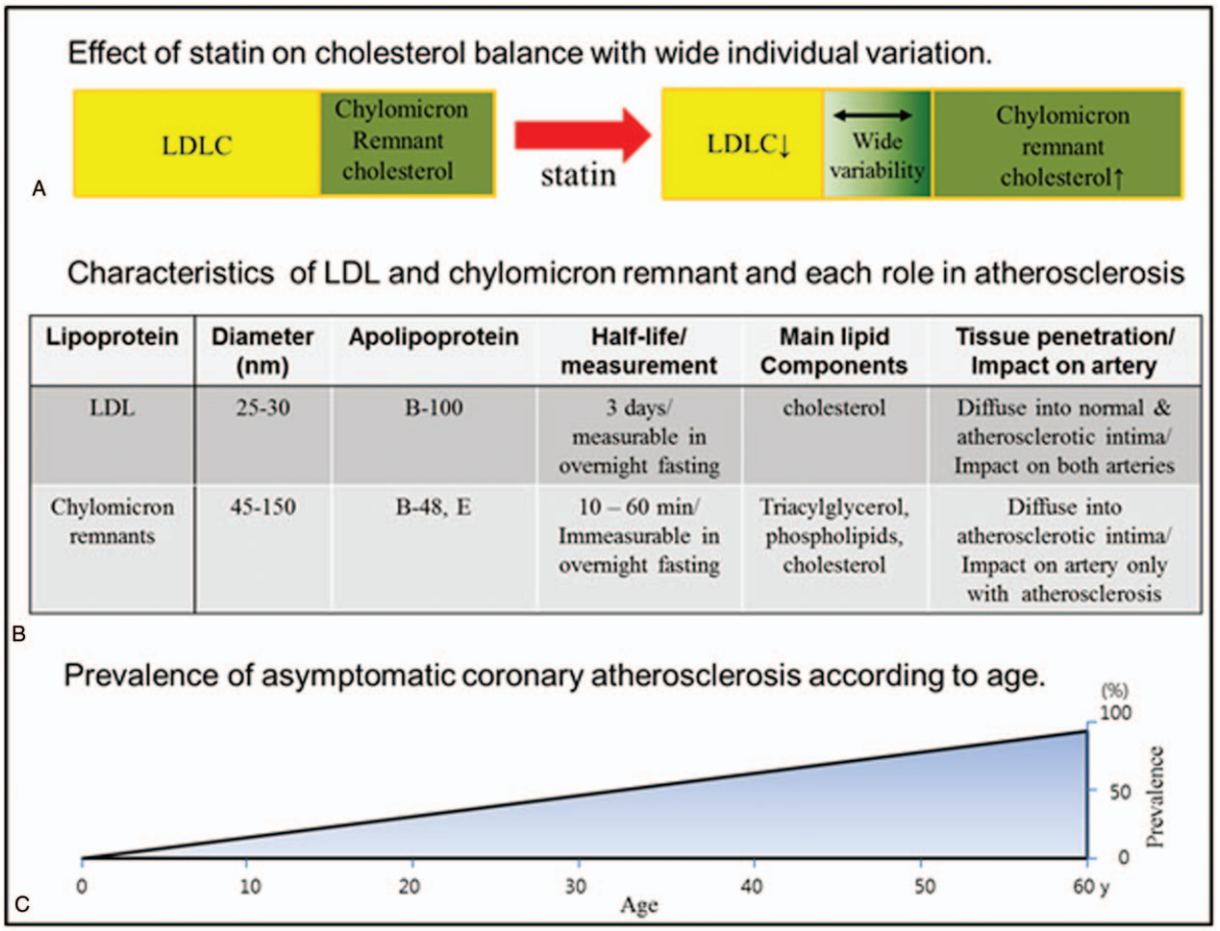
BMI = body mass index, BNP = B-type natriuretic peptide, DM = diabetes mellitus, eGFR = estimated glomerular filtration rate, hsCRP = high-sensitivity C-reactive protein, HTN = hypertension, LDL-C = low-density lipoprotein cholesterol, PCI = percutaneous coronary intervention.

Second, statins modify cholesterol balance between intestinal absorption and hepatic synthesis, in addition to LDL-C lowering.[21] When statins are administered, the hepatic-intestinal interaction is altered to increase intestinal cholesterol absorption.[22] While the amount of cholesterol in the blood consists of chylomicron cholesterol, chylomicron remnant cholesterol, LDL-C, and VLDL-C, only LDL-C level is used as a surrogate marker of the cholesterol burden of atherosclerosis in the arterial wall. Chylomicrons are not directly involved in atherogenesis because of their larger size and inability to efficiently penetrate arterial tissue in healthy subjects. However, several studies suggest that once chylomicrons are hydrolyzed to their remnant form, the triglyceride-depleted chylomicron remnants can penetrate arterial tissue and become preferentially trapped within the subendothelial space as concentrated foci in symptomatic and asymptomatic atherosclerotic subjects.[23] This appears to be related to the increased permeability of the

endothelial surface overlying the atherosclerotic plaque.[24] In a Mendelian randomized study, low cholesterol levels that resulted from the reduction of intestine-derived cholesterol had a preventive effect on clinical ASCVD outcomes, similar to the low cholesterol observed from the inhibition of hepatic synthesis.[17] Since atherosclerotic lesions are highly prevalent with aging,[25] it can be an important factor that complicates the association between LDL-C lowering and clinical outcome in statin therapy. In the subgroup analysis of the IMPROVE-IT study, the inhibition of intestinal cholesterol absorption by ezetimibe after statin therapy was effective for the prevention of CVD outcomes in older patients.[26] In another Mendelian study, the effect of ASCVD prevention with statin therapy was only one third of the benefit preventing ASCVD by genetic LDL-C reduction, despite of the same amount of LDL-C reduction after statin therapy.[27] This result suggests the occurrence of compensatory changes in cholesterol metabolism offsets in part the LDL-C lowering effect by statin therapy on ASCVD prevention as well as the short-term exposure effect of cholesterol lowering by statin administration.[27]

Despite these physiologic changes with statin therapy, we still measure only LDL-C levels in order to evaluate the cholesterol burden, even in statin users. Unfortunately, the measurement of LDL-C and chylomicron remnant cholesterol levels simultaneously is impossible because of the different half-lives of the lipoprotein cholesterols.[22,28] Statins could shift the proportion of dominant cholesterol-containing lipoprotein from LDL to chylomicron remnant, which is not detected by routine overnight fasting blood examination due to its very short half-life after meals (Fig. 4). Thus, a novel marker for representing true cholesterol burden in blood after statin therapy is needed. The LDL-C level in overnight fasting blood does not appear to be a proper marker of cholesterol burden with statin therapy. In order to measure the exact cholesterol burden in blood after statin therapy, we believe that chylomicron remnant cholesterol should be measured, in addition to LDL-C.

This study also has several limitations. First, a selection bias might have resulted from the prospective observational design, which utilized registry data from a single center. However, we performed a propensity score matching analysis to overcome unrecognized confounding factors. Another limitation is that the use of data on physician prescriptions to account for medications. We were unable to verify that the patients were actually taking their medications. Lastly, other cardiovascular events such as coronary artery bypass graft, specific cardiovascular related deaths, and hospitalization for heart failure are also needed to be



Lipoprotein	Diameter (nm)	Apolipoprotein	Half-life/ measurement	Main lipid Components	Tissue penetration/ Impact on artery
LDL	25-30	B-100	3 days/ measurable in overnight fasting	cholesterol	Diffuse into normal & atherosclerotic intima/ Impact on both arteries
Chylomicron remnants	45-150	B-48, E	10 – 60 min/ Immeasurable in overnight fasting	Triacylglycerol, phospholipids, cholesterol	Diffuse into atherosclerotic intima/ Impact on artery only with atherosclerosis

Figure 4. The proposed mechanisms of why the LDL cholesterol level is not a representative marker of cholesterol burden in atherosclerosis with the usual overnight fasting state in statin therapy. (A) The significance of chylomicron remnant cholesterol in cases of atherosclerosis is increasing, but it is immeasurable in overnight fasting blood due to a short half-life. (B) Statin change cholesterol metabolism increasing intestine-derived cholesterol level in blood, but the degree of this metabolic change is dependent on individual variability of genetic and environmental factors. (C) Prevalence of asymptomatic coronary atherosclerosis is increasing with age. Data modified from Tuzcu et al. [25] LDL = low-density lipoprotein, LDL-C = low-density lipoprotein cholesterol; →, decreased; ↔, variable; ↑, increased.

analyzed in the further studies to elucidate the relationship between statin responsiveness and cardiovascular outcomes. Despite these limitations, we believe that the preventive effect of statins is independent of the achieved LDL-C level. This result can relieve some of the concerns about whether cholesterol levels should be monitored during statin therapy in clinical practice. To the best to our knowledge, this is the first prospective matched cohort study, which investigated the association between achieved LDL-C levels and clinical ASCVD outcomes after statin therapy by comparing the normal cholesterol responders and non-responders. In the present study, we used propensity-score matched population and adjusted various potential confounders including statin intensity in order to clarify the statin-related cholesterol changes and clinical outcomes. The upcoming large, multicenter, prospective trials are required to demonstrate these findings.

In conclusion, there is substantial individual variability in the response to statin therapy, which is conventionally monitored by LDL-C levels. Given statin therapy, the benefits of ASCVD risk reduction may not related to LDL-C lowering or LDL-C goal based treatment. Therefore, the role of adherence to LDL-C goal based treatment to monitor ASCVD risk should be tailored for clinical practice after statin therapy.

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