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ORIGINAL ARTICLE

Population Science

Low-Density Lipoprotein Cholesterol Levels on Statins and Cardiovascular Event Risk in Stable Coronary Artery Disease
— An Observation From the REAL-CAD Study —

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Background: The relationship between very low on-treatment low-density lipoprotein cholesterol (LDL-C) level and cardiovascular event risk is still unclear in patients receiving the same doses of statins.

Methods and Results: From the REAL-CAD study comparing high-dose (4 mg/day) with low-dose (1 mg/day) pitavastatin therapy in patients with stable coronary artery disease, 11,105 patients with acceptable statin adherence were divided into 3 groups according to the on-treatment LDL-C level at 6 months (<70 mg/dL, 70–100 mg/dL, and ≥100 mg/dL). The primary outcome measure was a composite of cardiovascular death, non-fatal myocardial infarction, non-fatal ischemic stroke, or unstable angina requiring emergent admission. The adjusted risks of the LDL-C <70 mg/dL group relative to the LDL-C 70–100 mg/dL group (reference) was not significantly different for the primary outcome measure in both 1 mg/day and 4 mg/day strata (HR 0.84, 95% CI 0.58–1.18, P=0.32, and HR 1.25, 95% CI 0.88–1.79, P=0.22). The adjusted risk of the LDL-C ≥100 mg/dL group relative to the reference group was not significant for the primary outcome measure in the 1 mg/day stratum (HR 0.82, 95% CI 0.60–1.11, P=0.21), whereas it was highly significant in the 4 mg/day stratum (HR 3.32, 95% CI 2.08–5.17, P<0.001).

Conclusions: A very low on-treatment LDL-C level (<70 mg/dL) was not associated with lower cardiovascular event risk compared with moderately low on-treatment LDL-C level (70–100 mg/dL) in patients receiving the same doses of statins.

Key Words: Coronary artery disease; Lipids; Statin

L ipid-lowering therapy, statins therapy in particular, is the established fundamental secondary prevention strategy for patients with atherosclerotic cardiovascular disease.[1,2] Based on the results from several "more versus less statins" trials, the 2013 and 2018 American College of Cardiology (ACC)/American Heart Association (AHA) guidelines recommend high-intensity statin therapy for the secondary prevention or for patients with high risk of atherosclerotic disease regardless of the baseline low-density lipoprotein cholesterol (LDL-C) level without set-
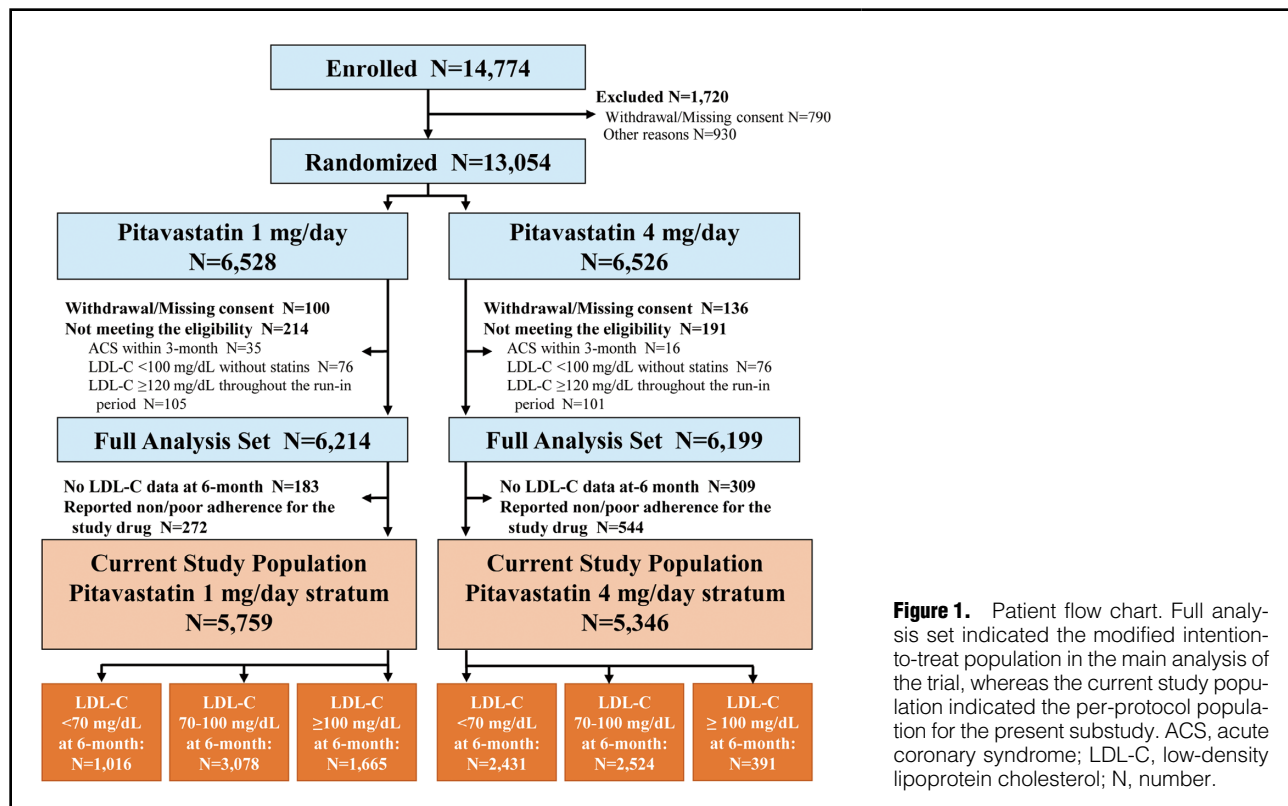
Figure 1. Patient flow chart. Full analysis set indicated the modified intention-to-treat population in the main analysis of the trial, whereas the current study population indicated the per-protocol population for the present substudy. ACS, acute coronary syndrome; LDL-C, low-density lipoprotein cholesterol; N, number.

ting a specific target LDL-C level.[1-4] In contrast, the 2019 European Society of Cardiology (ESC) guideline recommends a targeted LDL-C strategy aiming for an LDL-C target of <70mg/dL for patients at high cardiovascular risk.[5] One of the limitations of the target LDL-C strategy is the absence of adequate randomized trials that could confirm the optimal target LDL-C level. To adopt the target LDL-C strategy aiming for an LDL-C target of <70mg/dL, we should demonstrate that patients receiving on-treatment LDL-C below the target level are associated with a lower cardiovascular risk than patients receiving on-treatment LDL-C above the target level, independent of the risk factors, other than LDL-C, and the intensity of lipid-lowering therapy such as doses of statins. However, it is still uncertain whether the lower on-treatment LDL-C level in the range of a relatively low LDL-C level is independently associated with lower cardiovascular event risk.[6-8] Therefore, we sought to compare the cardiovascular event risk according to the on-treatment LDL-C levels in patients receiving the same doses of statins in the Randomized Evaluation of Aggressive or Moderate Lipid-Lowering Therapy with Pitavastatin in Coronary Artery Disease (REAL-CAD) trial.

Methods

The data, analytical methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

The design and the main results of the REAL-CAD trial were reported previously.[1] In brief, the REAL-CAD trial is a prospective, multicenter, randomized, open-label, blinded endpoint, physician-initiated superiority trial to explore whether high-dose pitavastatin (4mg/day) as compared with low-dose pitavastatin (1mg/day) could reduce cardiovascular events in Japanese patients with stable coronary artery disease. Enrolled patients received pitavastatin 1 mg once daily orally for a run-in period of at least 1 month. We excluded those patients with: (1) an LDL-C ≥120mg/dL throughout the run-in period; (2) onset of acute coronary syndrome and/or coronary revascularization within the past 3 months; and (3) occurrence of one of the following during the run-in period: poor adherence to pitavastatin, primary endpoint events, or other adverse events prohibiting study continuation. After the run-in period, eligible patients were randomized in a 1-to-1 fashion to receive either 4mg/day or 1mg/day oral pitavastatin.

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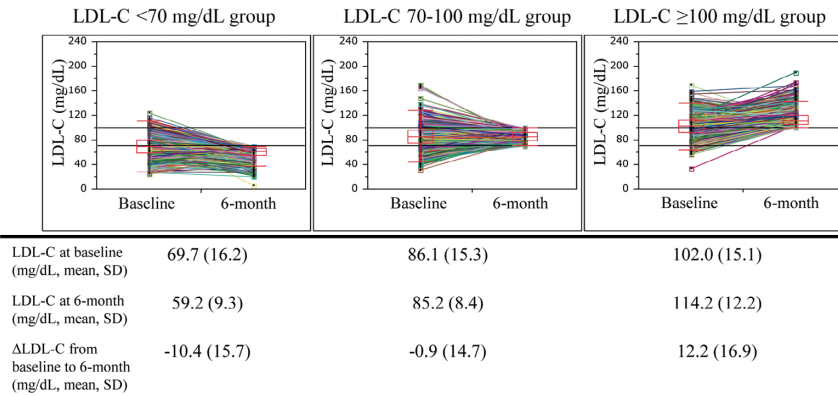
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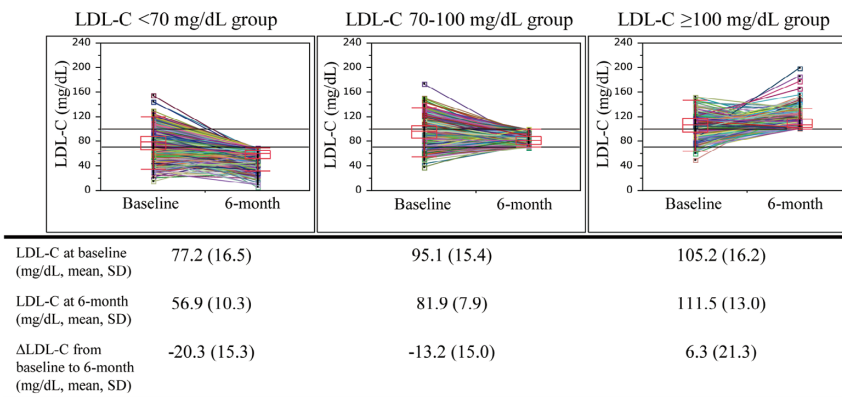
Figure 2. Serial changes in LDL-C level from baseline to 6 months follow up. (**A**) Pitavastatin 1 mg/day stratum. (**B**) Pitavastatin 4 mg/day stratum. LDL-C, low-density lipoprotein cholesterol; SD, standard deviation.

The present study was the post-hoc sub-study of the REAL-CAD study, and its analysis plan was reviewed and approved by the steering committee and the trial statistician. In this trial, 13,054 patients with an LDL-C <120 mg/dL on pitavastatin 1 mg/day at any time during the run-in period were randomized either to receive pitavastatin 1 mg/day or 4 mg/day. Among the full analysis set of 12,413 patients in the main study (modified intention-to-treat population), 11,921 patients had 6-month LDL-C data available for analysis. In an attempt to explore the causal relationship between the LDL-C levels on statins and cardiovascular event risk, we excluded 816 patients with reported non/poor adherence for the study drug during the initial 6 months after randomization, including 390 patients who discontinued the study drug or changed their study drug dose, and 426 patients with <75% drug adherence reported in the case report form (takes study drug <6 times per 1 week). Therefore, the current study population consisted of 11,105 patients (pitavastatin 1 mg/day stratum: 5,759 patients, and pitavastatin 4 mg/day stratum: 5,346 patients) without reported non-adherence for the study drug (per protocol population) (**Figure 1**). The patients were divided into the 3 groups according to their on-treatment LDL-C level at 6 months (<70 mg/dL, 70–100 mg/dL, and ≥100 mg/dL), stratified by the pitavastatin doses. The specific cut-off values for the on-treatment LDL-C level was decided based on the current and historical guideline recommendations.[3-5,9-11]
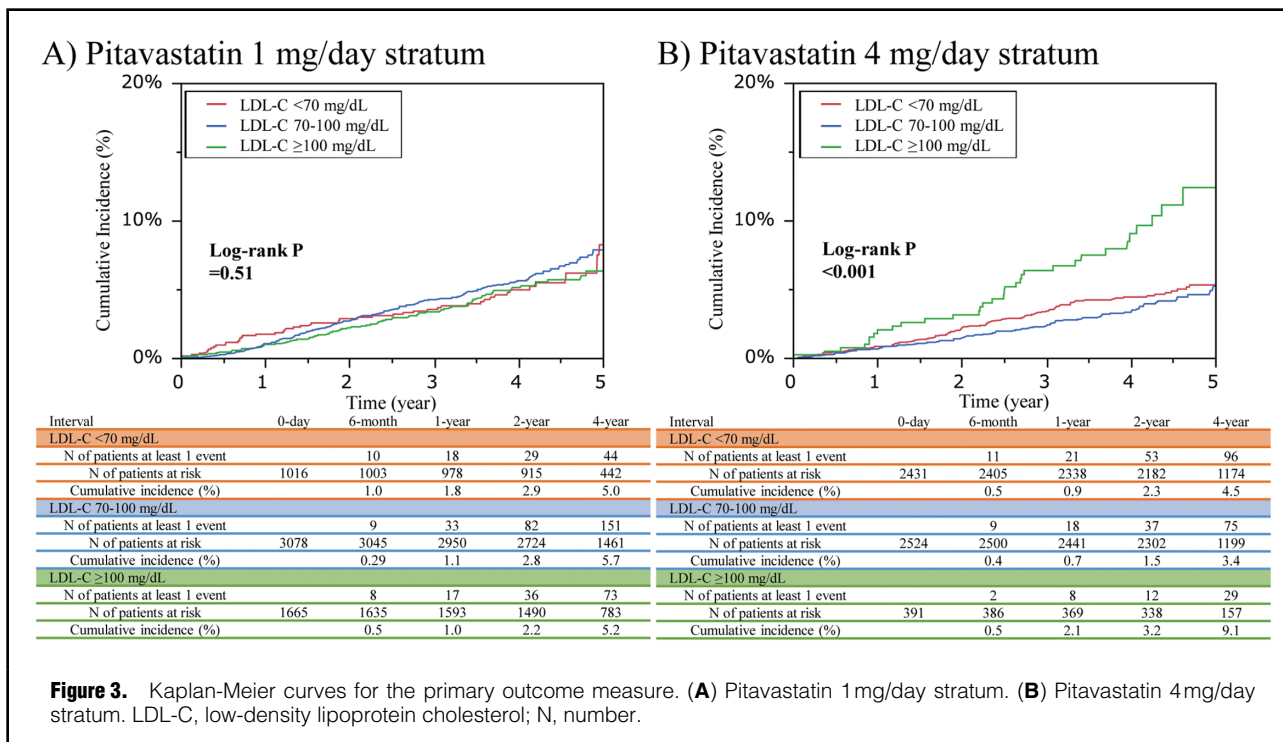
Serum lipid levels such as LDL-C, total cholesterol, triglyceride, and high-density lipoprotein cholesterol, as well as other blood tests such as creatine kinase, alanine aminotransferase, aspartate aminotransferase, creatinine, and hemoglobin A1c, were to be measured at baseline, at 6 and 12 months, and yearly thereafter, whereas high-sensitivity C-reactive protein was to be measured at baseline and at 6 months.

Values for LDL-C at baseline and at 6 months were derived from the central laboratory measurements using the Friedewald equation. If a value from the central laboratory measurements was missing or not calculable, a value obtained from the insurance-covered measurement was used instead. If this value was also missing, that value was not imputed from other data, but was handled as a missing value.

Primary outcome measure in the present analysis was a composite of cardiovascular death, non-fatal myocardial infarction, non-fatal ischemic stroke, or unstable angina requiring emergent admission and is consistent with the primary analysis of the trial.[1] The major secondary outcome measure was defined as a composite of the primary endpoint event or clinically indicated coronary revascularization, excluding target-lesion revascularization for lesions treated at a prior percutaneous coronary intervention.

Categorical variables are expressed as numbers and percentages. Continuous variables are shown as mean with

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Figure 3. Kaplan-Meier curves for the primary outcome measure. (**A**) Pitavastatin 1 mg/day stratum. (**B**) Pitavastatin 4 mg/day stratum. LDL-C, low-density lipoprotein cholesterol; N, number.

A) Pitavastatin 1 mg/day stratum

Interval	0-day	6-month	1-year	2-year	4-year
LDL-C <70 mg/dL					
N of patients at least 1 event		10	18	29	44
N of patients at risk	1016	1003	978	915	442
Cumulative incidence (%)		1.0	1.8	2.9	5.0
LDL-C 70-100 mg/dL					
N of patients at least 1 event		9	33	82	151
N of patients at risk	3078	3045	2950	2724	1461
Cumulative incidence (%)		0.29	1.1	2.8	5.7
LDL-C ≥100 mg/dL					
N of patients at least 1 event		8	17	36	73
N of patients at risk	1665	1635	1593	1490	783
Cumulative incidence (%)		0.5	1.0	2.2	5.2

B) Pitavastatin 4 mg/day stratum

Interval	0-day	6-month	1-year	2-year	4-year
LDL-C <70 mg/dL					
N of patients at least 1 event		11	21	53	96
N of patients at risk	2431	2405	2338	2182	1174
Cumulative incidence (%)		0.5	0.9	2.3	4.5
LDL-C 70-100 mg/dL					
N of patients at least 1 event		9	18	37	75
N of patients at risk	2524	2500	2441	2302	1199
Cumulative incidence (%)		0.4	0.7	1.5	3.4
LDL-C ≥100 mg/dL					
N of patients at least 1 event		2	8	12	29
N of patients at risk	391	386	369	338	157
Cumulative incidence (%)		0.5	2.1	3.2	9.1

standard deviation, or median and interquartile range. Missing data for other variables were not imputed and patients with such missing values were excluded from the analyses. We compared continuous variables with the one-way analysis of variance or the Kruskal-Wallis test according to their distributions. Categorical variables were analyzed with the chi-squared test. The cumulative incidence of clinical events was estimated from the baseline by using the Kaplan–Meier method and intergroup differences were compared by the log-rank test. The effects of on-treatment LDL-C <70 mg/dL or LDL-C ≥100 mg/dL relative to on-treatment LDL-C 70–100 mg/dL (reference) stratified by the pitavastatin doses were assessed by using the multivariable Cox proportional hazards models using dummy variables and was expressed as a hazard ratio and its 95% confidence interval. We selected 19 clinically relevant risk-adjusting variables listed in **Supplementary Table 1**; of note, the individual baseline LDL-C level was included as a covariate to assess the effects of on-treatment LDL-C value independent of the baseline LDL-C levels. We categorized age, body mass index, high-sensitivity C-reactive protein at 6 months, high-density lipoprotein cholesterol, and triglyceride by clinically meaningful reference values. Proportional hazards assumptions for the risk-adjusting variables, including the categorized LDL-C in quintiles, were assessed on the plots of log (time) vs. log (-log [survival]) stratified by the variables, and were judged to be acceptable.

We categorized the study patients by LDL-C levels at 6 months. Nevertheless, the follow-up evaluation for the clinical events was commenced on the day of randomization, because the lipid-lowering and pleiotrophic effects of statins are reported to emerge shortly after their administration.[12–14] As a sensitivity analysis, we performed 6-month landmark analyses for the primary outcome measure, excluding those patients with the endpoint events occurring within 6 months.

All the statistical analyses were conducted by a physician (Toshiaki Toyota) and a statistician (Takeshi Morimoto) using JMP version 10.0.2 (SAS Institute, Cary, NC, USA). All P values were 2-sided and P values <0.05 were considered statistically significant.

The study protocol was approved by the Public Health Research Foundation ethics review committee and by the ethics committees at all participating centers. All study patients provided written informed consent. The study was conducted in accordance with the Declaration of Helsinki. Trial registration: NCT01042730.

Results

Among the 11,105 study patients, on treatment LDL-C levels at 6 months were <70 mg/dL in 3,447 patients, 70–100 mg/dL in 5,602 patients, and ≥100 mg/dL in 2,056 patients. The patients in the pitavastatin 4 mg/day stratum were dominant in the on-treatment LDL-C <70 mg/dL group, whereas the patients in the pitavastatin 1 mg/day stratum were dominant in the on-treatment LDL-C ≥100 mg/dL group (**Supplementary Figure 1**). In the pitavastatin 1 mg/day stratum, on treatment LDL-C levels at 6 months were <70 mg/dL in 1,016 patients, 70–100 mg/dL in 3,078 patients, and ≥100 mg/dL in 1,665 patients, whereas in the pitavastatin 4 mg/day stratum, on treatment LDL-C levels at 6 months were <70 mg/dL in 2,431 patients, 70–100 mg/dL in 2,524 patients, and ≥100 mg/dL in 391 patients.

In both the pitavastatin 1 mg/day and 4 mg/day strata, LDL-C at baseline trended to be lower with decreasing on-treatment LDL-C at 6 months (**Figure 2**). In the pitavastatin 1 mg/day stratum, LDL-C decreased by −10.4 mg/dL in the LDL-C <70 mg/dL group, it was unchanged in the LDL-C 70–100 mg/dL group, and it increased by 12.2 mg/dL in the LDL-C ≥100 mg/dL group from baseline to 6 months (**Figure 2**). In the pitavastatin 4 mg/day stratum, LDL-C

Table. Clinical Outcomes

Outcomes	Number of patients with event (Cumulative 4-year incidence, n [%])			
	LDL-C <70 mg/dL	LDL-C 70–100 mg/dL	LDL-C ≥100 mg/dL	Log rank P value
Pitavastatin 1 mg/day stratum	N=1,016	N=3,078	N=1,665	
Primary outcome measure	44 (5.0)	151 (5.7)	73 (5.2)	0.51
Major secondary outcome measure	75 (8.4)	289 (10.7)	141 (9.7)	0.13
Pitavastatin 4 mg/day stratum	N=2,431	N=2,524	N=391	
Primary outcome measure	96 (4.5)	75 (3.4)	29 (9.1)	<0.001
Major secondary outcome measure	191 (8.8)	155 (6.9)	40 (12.5)	0.003

Outcomes	Risk of the LDL <70 mg/dL group relative to the LDL-C 70–100 mg/dL group			
	Unadjusted HR (95% CI)	P value	Adjusted HR (95% CI)	P value
Pitavastatin 1 mg/day stratum				
Primary outcome measure	0.93 (0.68–1.26)	0.65	0.84 (0.58–1.18)	0.32
Major secondary outcome measure	0.80 (0.63–1.02)	0.07	0.77 (0.58–1.01)	0.055
Pitavastatin 4 mg/day stratum				
Primary outcome measure	1.24 (0.93–1.65)	0.14	1.25 (0.88–1.79)	0.22
Major secondary outcome measure	1.25 (1.02–1.53)	0.03	1.20 (0.94–1.54)	0.15

Outcomes	Risk of the LDL-C ≥100 mg/dL group relative to the LDL-C 70–100 mg/dL group			
	Unadjusted HR (95% CI)	P value	Adjusted HR (95% CI)	P value
Pitavastatin 1 mg/day stratum				
Primary outcome measure	0.86 (0.66–1.11)	0.25	0.82 (0.60–1.11)	0.21
Major secondary outcome measure	0.87 (0.72–1.06)	0.17	0.83 (0.66–1.04)	0.11
Pitavastatin 4 mg/day stratum				
Primary outcome measure	2.61 (1.73–3.85)	<0.001	3.32 (2.08–5.17)	<0.001
Major secondary outcome measure	1.72 (1.22–2.37)	0.002	1.90 (1.29–2.73)	0.002

Primary outcome measure: a composite of cardiovascular death, non-fatal myocardial infarction, non-fatal ischemic stroke, or unstable angina requiring emergency hospitalization. Major secondary outcome measure: a composite of primary outcome measure or coronary revascularization. For the secondary composite endpoint, coronary revascularization excludes target-lesion revascularization for lesions treated at prior percutaneous coronary intervention. Cumulative 4-year incidence was estimated using the Kaplan-Meier method. CI, confidence interval; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol.
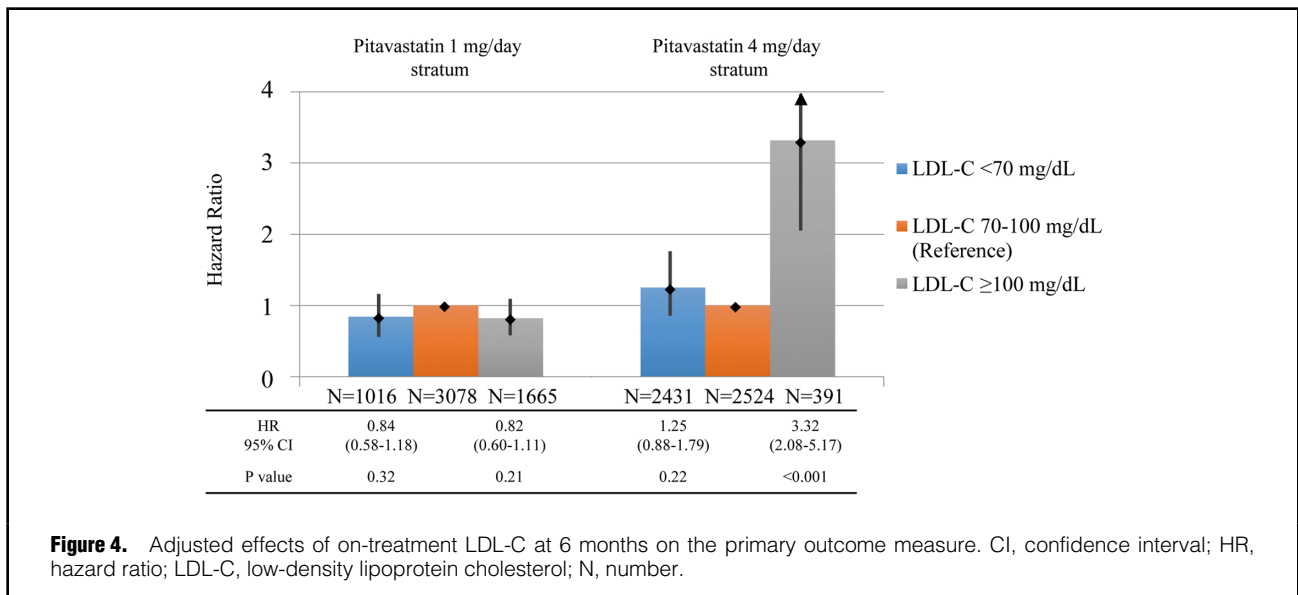

Figure 4. Adjusted effects of on-treatment LDL-C at 6 months on the primary outcome measure. CI, confidence interval; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; N, number.

decreased by −20.3 mg/dL in the LDL-C <70 mg/dL group, and by −13.2 mg/dL in the LDL-C 70–100 mg/dL group, whereas LDL-C increased by 6.3 mg/dL in the LDL-C ≥100 mg/dL group from baseline to 6 months despite dose escalation of pitavastatin from 1 mg/day to 4 mg/day after randomization (**Figure 2**).

In the pitavastatin 1 mg/day stratum, there were significant differences in age, sex, history of atrial fibrillation, stroke, diabetes, hypertension, chronic kidney disease, duration from acute coronary syndrome to randomization, duration from revascularization to randomization, and revascularization within 1 year before randomization across the 3 on-treatment LDL-C groups (**Supplementary Table 1**). In the pitavastatin 4 mg/day stratum, there were significant differences in age, sex, body mass index, abdominal circumference, history of stroke, chronic kidney disease, revascularization within 1 year before randomization, and use of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker across the 3 on-treatment LDL-C groups (**Supplementary Table 1**).

The median follow-up period for the survivors in the current study population was 4.0 (interquartile range, 3.1–4.7) years. In the pitavastatin 1 mg/day stratum, cumulative 4-year incidence of the primary outcome measure was not significantly different across the 3 on-treatment LDL-C groups (**Figure 3**, **Table**). After adjusting for confounders, the risks of the LDL-C <70 mg/dL group or the LDL-C ≥100 mg/dL group relative to the LDL-C 70–100 mg/dL group (reference) remained insignificant for the primary outcome measure. There was no apparent signal suggesting a positive relationship between on-treatment LDL levels and cardiovascular event risk (**Figure 4**, **Table**). In the pitavastatin 4 mg/day stratum, cumulative 4-year incidence of the primary outcome measure was significantly higher in the LDL-C ≥100 mg/dL group than in the LDL-C <70 mg/dL and 70–100 mg/dL groups (**Figure 3**, **Table**). After adjusting for confounders, the excess risk of the LDL-C ≥100 mg/dL group relative to the reference group remained significant for the primary outcome measure, whereas the risk of the LDL-C <70 mg/dL relative to the reference group was not significant for the primary outcome measure (**Figure 4**, **Table**). Therefore, patients with very low on-treatment LDL-C level (70 mg/dL) as compared with those with moderately low on-treatment LDL-C level (70–100 mg/dL) were not associated with lower risk for the primary outcome measure in both pitavastatin 1 mg/day and 4 mg/day strata.

The results for the major secondary outcome measure were fully consistent with the results for the primary outcome measure (**Table**, **Supplementary Figure 2**). The results for the sensitivity analysis starting at the 6-month landmark point were also fully consistent with the results of the main analysis (**Supplementary Table 2**, **Supplementary Figure 3**).

Discussion

The major findings of the present study were as follows: (1) very low on-treatment LDL-C level (<70 mg/dL) was not associated with lower cardiovascular event risk compared with moderately low on-treatment LDL-C level (70–100 mg/dL) in patients receiving the same doses of statins; (2) high LDL-C (≥100 mg/dL) was not associated with higher cardiovascular event risk compared with a moderately low LDL-C level (70–100 mg/dL) in the pitavastatin 1 mg/day stratum, whereas it was associated with signifi-

cantly higher risk in the 4 mg/day stratum; (3) however, in the small subgroup of LDL-C ≥100 mg/dL in the 4 mg/day stratum, LDL-C increased by 6.3 mg/dL from baseline to 6 months despite dose escalation of pitavastatin from 1 mg/day to 4 mg/day, suggesting the presence of unreported poor adherence.

"The lower the better" hypothesis for LDL-C level has been strengthened by the recent favorable observations from several non-statin lipid-lowering therapy trials.[15–17] "The lower the better" hypothesis is basically derived from the meta-regression analyses of randomized controlled trials of "statins versus placebo", "more versus less statins", and "non-statin lipid-lowering therapy versus placebo", suggesting that lower on-treatment LDL-C was associated with lower cardiovascular event rates.[18–20] However, the results from the meta-regression analyses might not be robust, because there are big differences in the risk profiles of the patients enrolled in the individual trials, and in the intensity of lipid-lowering therapy between the trial arms and across the trials. Therefore, it is still uncertain whether "the lower the better" hypothesis for the on-treatment LDL-C level, in the range of a relatively low LDL-C level, is applicable in patients receiving the same statin doses. A meta-analysis of 8 randomized controlled statin trials has suggested that patients who achieved very low LDL-C levels had a lower risk for major cardiovascular events than do those achieving moderately low LDL-C levels (LDL <50 vs. 75–<100: adjusted hazard ratio: 0.81, 95% confidence interval: 0.70–0.95).[6] However, they did not adjust for the intensity of statin therapy, which was reported to be closely associated with the magnitude of risk reduction with statins. It is very likely that patients with very low LDL-C levels had more often received high-intensity statin therapy than those with moderately low LDL-C levels. In contrast, a few real-world observational studies involving patients receiving statins suggested no incremental cardiovascular risk reduction in parallel with lower on-treatment LDL-C levels in the range <100 mg/dL.[7,8] The present study demonstrated that very low on-treatment LDL-C level (<70 mg/dL) was not associated with lower cardiovascular event risk, as compared with moderately low on-treatment LDL-C level (70–100 mg/dL) in patients receiving the same doses of statins. Furthermore, on-treatment LDL-C ≥100 mg/dL was not associated with higher cardiovascular event risk as compared with on-treatment LDL-C 70–100 mg/dL in the pitavastatin 1 mg/day stratum. The threshold LDL-C level that is independently associated with the higher risk for cardiovascular events might even be higher than the traditional target LDL-C level of <100 mg/dL. In the meantime, the small group of patients with on-treatment LDL-C ≥100 mg/dL in the pitavastatin 4 mg/day stratum were associated with markedly higher cardiovascular event risk as compared with patients with on-treatment LDL-C 70–100 mg/dL. However, the LDL-C level in this group of patients actually increased from baseline to 6 months despite escalation of pitavastatin dose from 1 mg/day to 4 mg/day, suggesting that unreported non-adherence to high-dose pitavastatin might be prevalent in this group of patients. Therefore, the markedly higher risk in this group of patients would not be due to the higher LDL-C level per se, but is due to the non-adherence to high-dose statin therapy, considering the absence of excess risk in the larger number of patients with on-treatment LDL-C ≥100 mg/dL in the pitavastatin 1 mg/day stratum. Some candidates in the pitavastatin 4 mg/dL group might

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have had unreported poor adherence from the run-in periods; it may explain the cause of apparently slight changes in LDL-C levels (6.3 mg/dL) in the LDL-C ≥100 mg/dL group despite the dose escalation. Expected decrease in LDL-C level by increasing the pitavastatin dose from 1 mg to 4 mg was expected to be 20%, and therefore, the actual 6.3 mg/dL increase in this subgroup was substantial. We could not find appropriate reasons for this increase in LDL-C level other than unreported non-adherence. In addition, the open-label design might have exacerbated underreporting of poor adherence and would have caused a nocebo effect in the pitavastatin 4 mg/day stratum. The low number of patients in the high LDL-C (≥100 mg/dL) group in the pitavastatin 4 mg/day stratum made it difficult to assess further detailed data. However, this observation might highlight the importance of good adherence to high-dose statin therapy. Furthermore, as the updated 2018 ACC/AHA guideline recommends, monitoring the LDL-C level rather than adopting the "fire and forget strategy" would be important to detect poor adherence in patients receiving high-dose statin therapy.

The target LDL-C strategy is very familiar for the practicing physicians. However, there are potential pitfalls in the target LDL-C strategy. Physicians may not prescribe high-dose statins for those statin-naïve patients with an LDL-C <70 mg/dL or for those patients having on-treatment LDL-C <70 mg/dL with low-dose statins, even if they have high cardiovascular event risk. This would not be a right practice, because previous "more versus less statins" trials clearly demonstrated the benefit of more intensive statin therapy in patients with atherosclerotic cardiovascular disease regardless of the LDL-C levels on low-dose statins.[1,2] Further, physicians may think of adding expensive non-statin lipid-lowering therapy for those patients having on-treatment LDL-C ≥70 mg/dL with high-dose statins, even if they have otherwise relatively low absolute cardiovascular event risk. The 2018 ACC/AHA guideline restricted the use of non-statin lipid-lowering therapy for patients with very high-risk of atherosclerotic cardiovascular disease. Meanwhile, the guideline also restricted the use of non-statin lipid-lowering therapy for patients with on-treatment LDL-C ≥70 mg/dL and treated with maximal statins. However, the reason for this recommendation for the LDL-C threshold is not because on-treatment LDL-C ≥70 mg/dL is a high-risk factor in itself, but simply because the pivotal studies of non-statin lipid-lowering therapy were conducted in patients with on-treatment LDL-C ≥70 mg/dL and treated with maximal statins.[15–17] The present study has important implications on the optimal lipid-lowering therapy strategy for patients with atherosclerotic cardiovascular disease. Too much emphasis on the target LDL-C strategy might mislead the clinical practice. As recommended in the 2018 ACC/AHA guideline, we should implement maximal statin therapy in most patients with atherosclerotic cardiovascular disease, irrespective of the baseline LDL-C levels. Non-statin lipid-lowering therapy should be considered based on the absolute residual risk of the individual patients treated with maximal statins therapy, and not based solely on the target LDL-C level.

The present study has some limitations. First, the study does not have adequate power to detect small differences in cardiovascular event risk according to the on-treatment LDL-C levels. We performed extensive statistical adjustment for confounders and obtained consistent results in the sensitivity analyses. Nevertheless, a post-hoc sub-study design precluded any definitive conclusions due to the unmeasured confounders. Second, adherence to the assigned pitavastatin therapy was not systematically monitored. In an attempt to explore the causal relationship between the on-treatment LDL-C level and cardiovascular event risk, we adopted the per-protocol analysis excluding those patients in whom poor adherence was reported. However, there was a strong signal suggesting the presence of unreported non-adherence, which might have had a strong influence on the present study results. Finally, patients were categorized based on the on-treatment LDL-C level at 6 months. We did not take the changes in LDL-C levels beyond 6 months into account; however, the treads of LDL-C levels were consistent among each group during follow up (**Supplementary Figure 4**).

Conclusions

Very low on-treatment LDL-C level (<70 mg/dL) was not associated with lower cardiovascular event risk compared with moderately low on-treatment LDL-C level (70–100 mg/dL) in patients receiving the same doses of statins. Too much emphasis on the target LDL-C strategy might mislead the clinical practice.

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Data Availability

The study data will not be made available.

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Supplementary Files

Please find supplementary file(s);
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