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Prognostic Implication of LDL-C Variability and Its Association with Lipid-Lowering Strategies: Insights from the RACING and LODESTAR Trials

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Purpose: We aimed to compare the visit-to-visit variability in low-density lipoprotein cholesterol (LDL-C) according to different lipid-lowering strategies and evaluate its prognostic implications using data from previous trials.

Materials and Methods: We analyzed two randomized clinical trials: the RACING trial and the LODESTAR trial. LDL-C variability was evaluated using standard deviation (SD), coefficient of variation, and variation independent of mean. The primary endpoint was a composite of death, myocardial infarction, stroke, or coronary revascularization.

Results: Among the 6800 patients included, when compared with patients randomized to high-intensity statins, LDL-C variability was similar in the group randomized to moderate-intensity statin plus ezetimibe combination, but it was higher in those randomized to treat-to-target strategy. The variability in LDL-C (by SD) was a predictor of primary endpoint even after adjustment for lipid-lowering strategy and mean LDL-C (hazard ratio 1.024; 95% confidence interval 1.014 to 1.035; $p<0.001$). Every 1-SD increase in LDL-C variability (SD) was also independently associated with higher risk of myocardial infarction by 2.1%, stroke by 3.5%, and coronary revascularization by 2.7%.

Conclusion: Compared to high-intensity statin therapy, LDL-C variability was not increased with the moderate-intensity statin plus ezetimibe combination therapy; however, it was increased in the treat-to-target strategy. Even among those treated with moderate- or high-intensity statins or statins with a target LDL-C levels of 50–70 mg/dL, increased LDL-C variability was associated with higher risk of adverse cardiovascular outcomes.

Key Words: Lipid-lowering therapy, cardiovascular outcome, low-density lipoprotein cholesterol, atherosclerotic cardiovascular disease

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INTRODUCTION

Increased intra-individual variability in biological measures, such as blood pressure, has been associated with poor cardiovascular outcomes.[1-4] Similarly, increased visit-to-visit variability in low-density lipoprotein cholesterol (LDL-C) levels has been independently associated with adverse cardiovascular events, including a higher risk of death.[5-8] These studies have also shown that high-intensity statin therapy lowers LDL-C variability compared to low-intensity statin therapy, suggesting a potential therapeutic benefit for managing LDL-C variability.[5]

Although intensive LDL-C reduction with high-intensity statin therapy is the recommended strategy among patients with established atherosclerotic cardiovascular disease (ASCVD),[9,10] the RACING (randomized comparison of efficacy and safety of lipid lowering with statin monotherapy versus statin-ezetimibe combination for high-risk cardiovascular disease) trial showed that moderate-intensity statin with ezetimibe combination therapy was noninferior to high-intensity statin monotherapy for the 3-year composite outcomes among patients with ASCVD.[11] Moreover, in the LODESTAR (low-density lipoprotein cholesterol-targeting statin therapy versus intensity-based statin therapy in patients with coronary artery disease) trial, treat-to-target strategy of 50 to 70 mg/dL as the goal was noninferior to a high-intensity statin therapy for the 3-year composite of death, myocardial infarction, stroke, or coronary revascularization in patients with coronary artery disease.[12] However, previous studies have not explored whether there are differences in LDL-C variability between these trials or the prognostic implications of such variability. Using data from these two trials, we aimed to compare the visit-to-visit variability in LDL-C according to different lipid-lowering strategies and evaluate the association of visit-to-visit variability and cardiovascular outcomes, particularly in patients treated with moderate- or high-intensity statins or statins targeting LDL-C levels of 50 to 70 mg/dL.

MATERIALS AND METHODS

The RACING and LODESTAR trials are registered with ClinicalTrials.gov under NCT03044665 and NCT02579499, respectively. The design and primary results of the RACING and LODESTAR trials have been previously reported.[11-13] Both trials were multicenter, randomized, active-controlled trials of lipid-lowering therapy with statins and ezetimibe. The RACING trial enrolled patients with documented ASCVD (previous myocardial infarction, acute coronary syndrome, history of coronary revascularization or other arterial revascularization procedures, ischemic stroke, or peripheral artery disease). In the LODESTAR trial, patients with clinically diagnosed coronary artery disease, including stable ischemic heart disease or acute coronary syndrome (unstable angina, acute myocardial infarction), were enrolled. Detailed inclusion and exclusion criteria of both trials are provided in the Supplementary Material (only online). The Institutional Review Board at each participating site approved the trial, and written informed consent was obtained from each patient (Yonsei University Health System IRB No. 4-4024-0253).

In the RACING trial, patients were randomized in a 1:1 ratio to receive either ezetimibe/moderate intensity statin combination therapy (rosuvastatin 10 mg with ezetimibe 10 mg once daily orally) or high-intensity statin monotherapy (rosuvastatin 20 mg once daily orally).[11] In the LODESTAR trial, patients were randomly assigned in a 1:1 ratio to receive either titrated-intensity statin therapy (treat-to-target) or high-intensity statin therapy.[12] In the treat-to-target group, statin intensity was titrated with a target LDL-C level of 50 to 70 mg/dL. For statin-naive patients, moderate-intensity statin therapy (atorvastatin 20 mg or rosuvastatin 10 mg) was initiated. For those who were already taking a statin, an equivalent intensity was maintained when the LDL-C level at randomization was below 70 mg/dL, and the intensity was up-titrated when the LDL-C level was 70 mg/dL or greater. During follow-up, in the treat-to-target group, up-titration for those with an LDL-C level of 70 mg/dL or greater, maintenance of the same intensity for those with an LDL-C level of 50 mg/dL or greater to less than 70 mg/dL, and down-titration for those with an LDL-C level less than 50 mg/dL was performed. In the high-intensity statin group, the maintenance of high-intensity statin therapy (atorvastatin 40 mg or rosuvastatin 20 mg) was recommended throughout the study period, without adjustment based on follow-up LDL-C levels.

Study population and definition

For this analysis, subjects with at least one post-baseline LDL-C measurement were included. Visit-to-visit variability in achieved LDL-C levels was evaluated using LDL-C measurements from 3 months after random assignment, as this was the period in which the LDL-C levels in the two treatment arms were relatively stable after the initial decrease.[5] Visit-to-visit LDL-C variability was defined as intra-individual variability in LDL-C values between visits. For patients with missing LDL-C values at any visit, the closest available LDL-C data were used to calculate LDL-C variability. Various measurements of variability were used: 1) the standard deviation (SD) of LDL-C levels; 2) coefficient of variation (CV); and 3) variability independent of the mean (VIM).[5-8] VIM was calculated as $100\times SD/mean^{beta}$, where beta is the regression coefficient, based on the natural logarithm of SD divided by the natural logarithm of the mean. In addition, this uncorrected VIM was corrected by using the following formula:

[VIM uncorrected×(mean of CV)]/(mean of VIM uncorrected).

In both trials, the follow-up schedule and study endpoints were largely similar.[11-13] In the RACING trial, patients were

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scheduled for follow-up visits at 2 and 6 months and every 1 year thereafter. In the LODESTAR trial, patients were scheduled for follow-up visits at 6 weeks and 3, 6, 12, 24, and 36 months. In both trials, at every visit, assessments were conducted on general health status, muscle-related symptoms, medication use, and the occurrence of an endpoint or adverse events. Serial follow-up of the patients' lipid profiles, including total cholesterol, LDL-C, high-density lipoprotein cholesterol, and triglyceride concentrations, were done at 1, 2, and 3 years in both trials. The primary end point was major adverse cardiac and cerebrovascular events, defined as a composite of all-cause death, myocardial infarction, stroke, and any coronary revascularization at 3 years, which was identical to the primary endpoint of the LODESTAR trial.[12] In addition, each individual endpoint of this primary endpoint was all identically evaluated in the RACING trial.[11] Death was classified as cardiovascular death and non-cardiovascular death. Cardiovascular death was defined as death due to myocardial infarction, sudden cardiac death, heart failure, stroke, cardiovascular procedures, cardiovascular hemorrhage, or any death where a cardiovascular cause could not be excluded, as adjudicated by the clinical endpoints committee.[14] Myocardial infarction was defined based on clinical symptoms, electrocardiographic changes, or abnormal findings during imaging studies, combined with an increase in the creatine kinase myocardial band fraction above the upper normal limit or an increase in the troponin-T or troponin-I level greater than the 99th percentile of the upper normal limit.[15] Stroke was defined as an acute cerebrovascular event resulting in a neurologic deficit for longer than 24 hours or the presence of an acute infarction in imaging studies.[16] Any coronary revascularization included percutaneous coronary intervention or coronary artery bypass graft surgery. Clinically indicated revascularization was defined as an invasive angiographic percent diameter stenosis of 50% or greater with ischemic symptoms or signs, or a percent diameter stenosis of 70% or greater, even in the absence of symptoms or signs.[14] Staged coronary revascularizations planned at randomization were not considered as adverse events. Key secondary endpoints included individual endpoints of the primary endpoint: all-cause death, myocardial infarction, stroke, and any coronary revascularization. Another secondary endpoint was cardiovascular death.

Statistical analysis

The Cox proportional hazards regression model was used to evaluate the relationship between LDL-C variability measurements and the risk of primary and secondary outcomes for the overall population. Three different models were used to calculate the hazard ratio (HR) for primary and secondary outcomes per 1-SD increase in LDL-C variability: Model 1 was unadjusted, using LDL-C variability as a continuous variable; Model 2 adjusted Model 1 for strategies of lipid-lowering therapy as a categorical variable with three levels (moderate-intensity statin plus ezetimibe combination therapy, treat-to-target strategy, and high-intensity statin therapy); and Model 3 adjusted Model 2 for mean LDL-C values (continuous). In addition, to evaluate the association between LDL-C variability and clinical outcomes (primary endpoint) visually, a restricted cubic spline regression model was generated with four knots at the 5th, 35th, 65th, 95th percentiles of LDL-C variability measures (reference is the 5th percentile) with an adjustment of lipid-lowering strategy and mean LDL-C levels. To assess the robustness of the results, the following sensitivity analyses were performed. Since LDL-C levels can be influenced by patient medication adherence, the analyses were performed after excluding the patients who did not receive the allocated therapy (in the per-protocol population), as well as those who discontinued or reduced the dose of the study drug due to intolerance. Details of the excluded patients in the per-protocol population in both trials are provided in the Supplementary Material (only online). In addition, to determine whether the risk varied over time, a sensitivity analysis was conducted that incorporated follow-up LDL-C levels as time-varying covariates.

RESULTS

Baseline characteristics

Among 3780 patients from the RACING trial and 4400 patients from the LODESTAR trial, 3093 patients and 3707 patients, respectively, had at least one post-baseline lipid measurement. Therefore, a total of 6800 patients were finally included in this analysis. Baseline characteristics of the overall population and according to lipid-lowering strategies in each trial are presented in Table 1. The mean age was 64 years, and 27% of the patients were women. Baseline LDL-C level was 81±32 mg/dL.

Study outcomes

Visit-to-visit variability in LDL-C according to lipid-lowering strategies from each trial are presented in Table 2. In the population from the RACING trial, visit-to-visit LDL-C variability was not different between the patients with moderate-intensity statin plus ezetimibe combination therapy and those with high-intensity statin monotherapy for all three measures (SD 9.17±7.34 vs. 8.92±7.15, p=0.325; CV 14.60±11.33 vs. 14.80±11.63, p=0.630; VIM 14.75±11.07 vs. 14.64±10.99, p=0.790) (Fig. 1). However, in the population from the LODESTAR trial, visit-to-visit LDL-C variability was significantly higher in the patients with treat-to-target strategy compared to those with high-intensity statin therapy (SD 10.55±7.66 vs. 8.92±7.15, p=0.001; CV 15.55±10.30 vs. 14.20±9.72, p<0.001; VIM 15.55±10.28 vs. 14.20±9.72, p<0.001) (Table 2 and Fig. 1). The average successive variability, which was defined as the average absolute difference between successive values, is also provided in Table 2.

During follow-up, among 6800 patients, 10 patients (0.1%) withdrew consent and 9 patients (0.1%) were lost to follow-up.

Table 1. Baseline Characteristics of Subjects with at Least One Post-Baseline LDL-C Measurement

	Overall population (n=6800)	Population from the RACING trial			Population from the LODESTAR trial		
		Moderate-intensity statin plus ezetimibe (n=1557)	High-intensity statin (n=1536)	*p*	Treat-to-target strategy (n=1857)	High-intensity statin (n=1850)	*p*
Age, yr	64±10	63±9	64±10	0.036	65±10	65±10	0.397
Women	1812 (26.6)	391 (25.1)	389 (25.3)	0.891	524 (28.2)	508 (27.5)	0.607
Height, cm	165±8	165±8	165±8	0.084	165±8	165±8	0.874
Weight, kg	68±11	69±11	68±11	0.192	67±11	67±11	0.806
Body mass index, kg/m^2	25±3	25±3	25±3	0.820	25±3	25±3	0.681
Prior percutaneous coronary intervention	4154 (61.1)	1045 (67.1)	1036 (67.4)	0.844	1046 (56.3)	1027 (55.5)	0.618
Prior coronary bypass graft surgery	506 (7.4)	111 (7.1)	9.3 (6.1)	0.229	141 (7.6)	161 (8.7)	0.217
Prior stroke	411 (6.0)	90 (5.8)	93 (6.1)	0.746	118 (6.4)	110 (5.9)	0.605
Hypertension	4510 (66.3)	1023 (65.7)	1027 (66.9)	0.496	1239 (66.7)	1221 (66.6)	0.642
Chronic kidney disease	608 (8.9)	169 (10.9)	168 (10.9)	0.941	133 (7.2)	138 (7.5)	0.728
End-stage kidney disease on dialysis	42 (0.6)	10 (0.6)	11 (0.7)	0.802	9 (0.5)	12 (0.6)	0.506
Diabetes mellitus	2400 (35.3)	590 (37.9)	557 (36.3)	0.348	621 (33.4)	632 (34.2)	0.643
Diabetes mellitus on insulin treatment	232 (3.4)	39 (2.5)	58 (3.8)	0.043	67 (3.6)	68 (3.7)	0.912
Dyslipidemia	6362 (93.6)	1489 (95.6)	1475 (96.0)	0.582	1699 (91.5)	1699 (91.8)	0.703
Current smoker	951 (14.0)	254 (16.3)	230 (15.0)	0.305	242 (13.0)	225 (12.2)	0.425
Baseline lipid profile, mg/dL							
TC	154±37	151±35	152±36	0.279	156±38	158±38	0.101
LDL-C	81±32	75±30	76±32	0.561	85±32	87±32	0.208
HDL-C	47±12	47±12	48±14	0.063	47±12	47±11	0.278
Triglyceride	139±82	141±81	138±76	0.381	139±85	138±84	0.728

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LODESTAR, low-density lipoprotein cholesterol-targeting statin therapy versus intensity-based statin therapy in patients with coronary artery disease; RACING, randomized comparison of efficacy and safety of lipid lowering with statin monotherapy versus statin-ezetimibe combination for high-risk cardiovascular disease; TC, total cholesterol.
Values are mean±SD or n (%).

Table 2. Comparison of Visit-to-Visit Variability in LDL-C According to Lipid-Lowering Strategies

	Population from the RACING trial			Population from the LODESTAR trial		
	Moderate-intensity statin plus ezetimibe (n=1557)	High-intensity statin (n=1536)	*p*	Treat-to-target strategy (n=1857)	High-intensity statin (n=1850)	*p*
Standard deviation	9.17±7.34	8.92±7.15	0.325	10.55±7.66	8.92±7.15	0.001
Coefficient of variation	14.60±11.33	14.80±11.63	0.630	15.55±10.30	14.20±9.72	<0.001
Variability independent of the mean	14.75±11.07	14.64±10.99	0.790	15.55±10.28	14.20±9.72	<0.001
Average successive variability	11.10±9.87	10.66±9.23	0.205	8.60±6.91	7.81±6.56	<0.001

LODESTAR, low-density lipoprotein cholesterol-targeting statin therapy versus intensity-based statin therapy in patients with coronary artery disease; RACING, randomized comparison of efficacy and safety of lipid lowering with statin monotherapy versus statin-ezetimibe combination for high-risk cardiovascular disease.
Values are mean±SD.

A total of 6781 patients (99.7%) completed the 3-year follow-up. At 3 years, among a total of 6800 patients, the primary endpoint occurred in 506 patients (7.47%). A restricted cubic spline regression model showed that variability in LDL-C, measured by SD, had a positive linear relationship with the occurrence of the primary endpoint (Fig. 2A). The other measures of variability in LDL-C, such as CV, and VIM also showed a consistent positive relationship with the primary endpoint (Fig. 2B and 2C). An increase in 1-SD of SD, CV, and VIM was associated with a higher risk of primary endpoint with a HR of 1.021 [95% confidence interval (CI) 1.011 to 1.031; $p<0.001$], 1.016 (95% CI 1.009 to 1.023; $p<0.001$), and 1.018 (95% CI 1.011 to 1.025; $p<0.001$), respectively (Table 3). In adjusted models, one with lipid-lowering strategy alone and another with both lipid-lowering strategy and mean LDL-C levels, these findings remained consistent. At 3 years, all-cause death and cardiovascular death occurred in 60 patients (0.88%) and 17 patients (0.25%), respectively. There was no significant association be-

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tween variability in LDL-C and all-cause of death in the unadjusted and adjusted models (Table 3). There was no significant association between variability in LDL-C and cardiovascular death in the unadjusted and adjusted models. When we analyzed the direction of LDL-C variability, 3564 patients had upward direction, whereas 3236 patients had downward direction. These two subgroups consistently showed a significant association between LDL-C variability and primary outcomes (HR 1.021; 95% CI 1.008 to 1.034; p=0.002 and HR 1.021; 95% CI 1.006 to 1.036; p=0.007).

Myocardial infarction occurred in 307 patients (4.53%) at 3 years for the overall population. Every 1-SD increase in LDL-C variability (SD) was associated with a 1.5% increase in myocardial infarction (HR 1.015; 95% CI 1.001 to 1.028; p=0.032) in the unadjusted model, a 1.5% increase in the adjusted model with lipid-lowering strategy, and a 2.1% increase in the fully adjusted model (Table 3). Results were consistent for CV and VIM in the fully adjusted models. During 3 years of follow-up, 49 patients (0.72%) experienced a stroke. Every 1-SD increase of LDL-C variability (SD) was associated with 3.7% increase in stroke (HR 1.037; 95% CI 1.010 to 1.065, p=0.006) in the unadjusted model. In both the adjusted model with lipid-lowering strategy and the fully adjusted model with mean LDL-C levels, the results remained consistent (HR 1.037; 95% CI 1.011 to 1.065; p=0.006; and HR 1.035; 95% CI 1.006 to 1.066; p=0.019). For other measures of variability in LDL-C, CV, and VIM, there were also significant association with stroke in both unadjusted and adjusted models. At 3 years, coronary revascularization was required in 360 patients (5.32%). In the unadjusted model, every 1-SD increase in LDL-C variability (SD) was associated with a 2.3% increase in coronary revascularization (HR 1.023; 95% CI 1.011 to 1.034; p<0.001). Similarly, in the adjusted models, LDL-C variability (SD) was significantly associated with an increase in the need for coronary revascularization (HR 1.023; 95% CI 1.011 to 1.034, p<0.001; and HR 1.027; 95% CI 1.014 to 1.039; p<0.001). There were also significant associations between other measures of LDL-C variability, such as the CV and VIM, and coronary revascularization in both unadjusted and adjusted models (Table 3).

Analysis confined to subjects in the per-protocol population also revealed similar results (Supplementary Table 1, only online). After excluding the patients who discontinued or reduced the dose of the study drug, the results were largely similar (Supplementary Table 2, only online). A sensitivity analysis that incorporated follow-up LDL-C levels as time-varying covariates showed consistent results (Supplementary Table 3, only online).

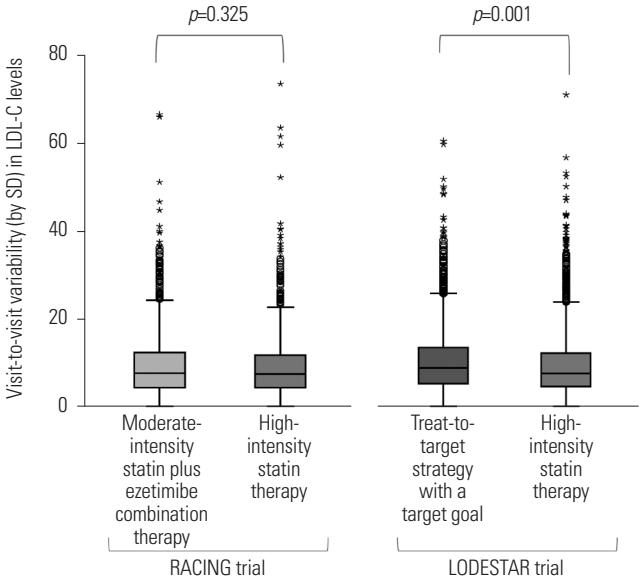

Fig. 1. Visit-to-visit variabilities in LDL-C according to lipid-lowering strategies. Compared to high-intensity statin therapy, visit-to-visit variability in LDL-C was not increased in the moderate-intensity statin plus ezetimibe combination therapy, but it was increased in the treat-to-target strategy. LDL-C, low-density lipoprotein cholesterol.

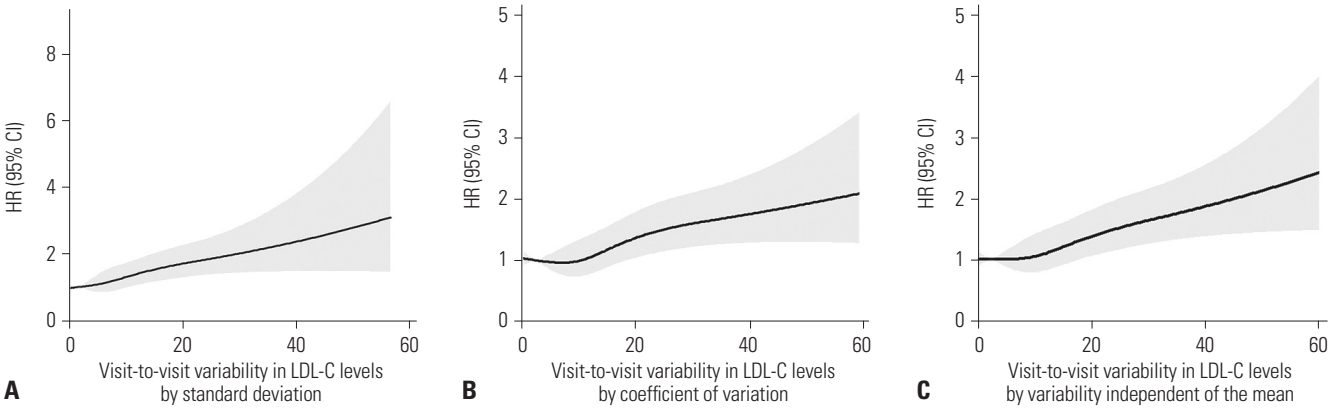

Fig. 2. Association between visit-to-visit variability in LDL-C and primary endpoint. In a restricted cubic spline regression model, graphs show HRs for the primary endpoint (a composite of all-cause death, myocardial infarction, stroke, or coronary revascularization) according to visit-to-visit variability in LDL-C; standard deviation (A), coefficient of variation (B), and variability independent of the mean (C). In this model, lipid-lowering strategy and mean LDL-C levels were adjusted. Data were fitted by a restricted cubic spline Cox proportional hazards regression model, and the model was conducted with four knots at the 5th, 35th, 65th, 95th percentiles of CV (reference is the 5th percentile). Solid lines indicate HRs, and shadow shapes indicate 95% CIs. HR, hazard ratio; CI, confidence interval; CV, coefficient of variation.

Table 3. Association between Visit-to-Visit Variability in LDL-C and Cardiovascular Outcomes

	Unadjusted model			Adjusted for lipid-lowering strategy			Adjusted for lipid-lowering strategy and mean LDL-C level		
	HR	95% CI	*p*	HR	95% CI	*p*	HR	95% CI	*p*
Primary endpoint									
Standard deviation	1.021	1.011 to 1.031	<0.001	1.021	1.011 to 1.031	<0.001	1.024	1.014 to 1.035	<0.001
Coefficient of variation	1.016	1.009 to 1.023	<0.001	1.016	1.009 to 1.023	<0.001	1.016	1.009 to 1.023	<0.001
Variability independent of the mean	1.018	1.011 to 1.025	<0.001	1.018	1.011 to 1.025	<0.001	1.018	1.011 to 1.025	<0.001
All-cause death									
Standard deviation	0.976	0.937 to 1.015	0.225	0.976	0.937 to 1.015	0.226	0.983	0.943 to 1.025	0.419
Coefficient of variation	1.006	0.984 to 1.029	0.604	1.006	0.984 to 1.029	0.600	1.004	0.982 to 1.027	0.716
Variability independent of the mean	1.003	0.979 to 1.027	0.824	1.003	0.979 to 1.027	0.818	1.003	0.980 to 1.027	0.779
Cardiovascular death									
Standard deviation	0.985	0.918 to 1.057	0.683	0.985	0.918 to 1.057	0.682	1.000	0.929 to 1.077	0.996
Coefficient of variation	1.013	0.975 to 1.052	0.512	1.013	0.975 to 1.052	0.513	1.009	0.972 to 1.048	0.638
Variability independent of the mean	1.012	0.972 to 1.054	0.560	1.012	0.972 to 1.054	0.563	1.013	0.972 to 1.055	0.541
Myocardial infarction									
Standard deviation	1.015	1.001 to 1.028	0.032	1.015	1.001 to 1.028	0.033	1.021	1.007 to 1.036	0.004
Coefficient of variation	1.016	1.008 to 1.025	<0.001	1.016	1.007 to 1.025	<0.001	1.015	1.006 to 1.024	0.001
Variability independent of the mean	1.018	1.009 to 1.027	<0.001	1.017	1.008 to 1.026	<0.001	1.018	1.008 to 1.027	<0.001
Stroke									
Standard deviation	1.037	1.010 to 1.065	0.006	1.037	1.011 to 1.065	0.006	1.035	1.006 to 1.066	0.019
Coefficient of variation	1.025	1.006 to 1.044	0.011	1.025	1.006 to 1.044	0.010	1.026	1.007 to 1.046	0.007
Variability independent of the mean	1.028	1.008 to 1.049	0.006	1.029	1.008 to 1.049	0.005	1.028	1.008 to 1.048	0.007
Coronary revascularization									
Standard deviation	1.023	1.011 to 1.034	<0.001	1.023	1.011 to 1.034	<0.001	1.027	1.014 to 1.039	<0.001
Coefficient of variation	1.017	1.009 to 1.025	<0.001	1.017	1.010 to 1.025	<0.001	1.018	1.010 to 1.026	<0.001
Variability independent of the mean	1.019	1.010 to 1.027	<0.001	1.019	1.010 to 1.027	<0.001	1.019	1.010 to 1.027	<0.001

CI, confidence interval; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol.
Primary endpoint was defined as a composite of all-cause death, myocardial infarction, stroke, or coronary revascularization.

DISCUSSION

The principle findings of this study are that: 1) compared to high-intensity statin monotherapy, moderate-intensity statin plus ezetimibe combination therapy did not increase visit-to-visit LDL-C variability; 2) the treat-to-target strategy, compared to high-intensity statin therapy with a target goal, increased visit-to-visit LDL-C variability; 3) increased visit-to-visit LDL-C variability was associated with adverse cardiovascular outcomes—a composite of all-cause death, myocardial infarction, stroke, or coronary revascularization—among patients with ASCVD, even in patients treated with moderate- or high-intensity statins or statins targeting LDL-C levels of 50 to 70 mg/dL. These findings were consistent after adjustment for lipid-lowering strategies and mean LDL-C levels and in the sensitivity analyses; and 4) although increase in LDL-C variability was not associated with an increased risk of all-cause death or cardiovascular death (likely due to overall low event rates), it was significantly related to an increased risk of myocardial infarction, stroke, or coronary revascularization.

Among patients with established ASCVD, it is well known that adverse cardiovascular events can be reduced when risk factors such as hypertension, dyslipidemia, smoking, inactivity, and obesity are well controlled.[1] In addition to controlling the magnitude of an individual risk factor, several studies have suggested that increased intra-individual variability in biological measures, such as blood pressure, is associated with all-cause mortality, cardiovascular death, or stroke.[2-4] Although LDL-C reduction with statin therapy is the main treatment for established ASCVD, few studies have evaluated the association between variability in LDL-C levels and cardiovascular outcomes. In the TNT (Treating to New Targets) trial with 9572 patients with CAD,[5] every 1-SD increase in LDL-C variability independently increased the risk of any coronary event by 16%, any cardiovascular event by 11%, death by 23%, myocardial infarction by 10%, and stroke by 17%. Similarly, in an analysis from the IDEAL (the Incremental Decrease in End Points Through Aggressive Lipid-Lowering) trial of 8658 patients with prior MI, every 1-SD increase in LDL-C variability independently increased the risk of any coronary event by 7%, any cardiovascular event by 8%, MI by 11%, and death by 20%.[6] Therefore, our current findings of a significant association between LDL-C vari-

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ability and primary outcome (a composite of all-cause death, myocardial infarction, stroke, and coronary revascularization) are consistent with previous studies. However, unlike the TNT trial (which compared high- vs. low-intensity statins),[5] in this analysis, we exclusively included patients treated with moderate- or high-intensity statins or statins targeting LDL-C levels of 50 to 70 mg/dL. Moreover, the baseline LDL-C in our study was lower than that in the TNT trial (81 mg/dL vs. 98 mg/dL).[17] Despite these differences, LDL-C variability remained a strong and independent predictor of adverse cardiovascular outcomes.

In our study, the relative increase in adverse cardiovascular events with higher LDL-C variability was somewhat lower than that reported in the prior studies (for example, only a 2.4% increase in primary outcome for every 1-SD increase in LDL-C variability). This may be attributed to the following reasons. Firstly, the follow-up duration was relatively shorter compared to previous studies. In the TNT trial, the median follow-up duration was 4.9 years.[17] In this analysis of the RACING and LODESTAR trials, the follow-up period for patients ended at 3 years.[11,12] Secondly, in the RACING trial, patients randomized to moderate-intensity statin therapy plus ezetimibe had lower LDL-C compared to those randomized to a high-intensity statin therapy. The achievement of LDL-C <70 mg/dL was also greater in the moderate-intensity statin therapy plus ezetimibe combination therapy.[10] In the TNT trial, the mean LDL-C levels during the study were 77 mg/dL among patients receiving 80 mg of atorvastatin and 101 mg/dL among those receiving 10 mg of atorvastatin.[17] In our study, the mean LDL-C level was 66.3±19.3 mg/dL due to a greater use of higher-intensity statin and combination with ezetimibe treatment. The shorter follow-up period, combined with lower LDL-C achieved, likely resulted in lower event rates compared to prior trials, potentially explaining the lower relative increase in adverse cardiovascular events associated with higher LDL-C variability observed in this study. Nevertheless, variability in LDL-C levels was significantly associated with poor cardiovascular outcomes, even though the mean LDL-C levels achieved were lower than those in previous studies. Therefore, in clinical practice, detection and recognition of high LDL-C variability through regular LDL-C monitoring may be important, although it is still unclear whether lower LDL-C variability improves prognosis. The possible biological mechanisms linking LDL-C variability to fewer cardiovascular events suggest that maintaining consistently low LDL-C levels with minimal fluctuation is associated with further reduction in plasma LDL-C levels through upregulation of cellular LDL receptors.[18]

Another important finding of this study was that visit-to-visit variability in LDL-C is affected by lipid-lowering strategies. In both the TNT and IDEAL trials, high-intensity statin therapy reduced visit-to-visit variability in LDL-C compared to low-intensity statin therapy.[5,6] Our findings from the LODESTAR trial, which demonstrated higher LDL-C variability in the treat-to-target strategy compared to high-intensity statin therapy, are consistent with the above findings. In the treat-to-target strategy of the LODESTAR trial, moderate-intensity and high-intensity dosing were used in 43% and 54%, respectively, and ezetimibe was used only <20%. On the other hand, findings from the RACING trial showed no difference in visit-to-visit variability in LDL-C with the moderate-intensity statin ezetimibe combination therapy compared to high-intensity statins. Taken together, the findings from this study suggest that LDL-C variability has prognostic implications and can be reduced either by high-intensity statins or a combination of moderate-intensity statin and ezetimibe.

This study has several limitations. First, this study used data from randomized clinical trials, and as such, may not fully reflect real-world practice. The variability in LDL-C levels in real world practice might be more pronounced. Second, the follow-up duration was relatively short in both trials; therefore, longer follow-ups are needed. Third, since this study exclusively included patients with ASCVD, the results may not be applicable to other patients' subsets, including those on statin therapy for primary prevention. Thus, future investigations should include broader populations.

In conclusion, compared to high-intensity statin therapy, the visit-to-visit variability in LDL-C was not increased with moderate-intensity statin plus ezetimibe combination therapy, but it was increased in the treat-to-target strategy targeting LDL-C levels of 50 to 70 mg/dL. Increased LDL-C variability was associated with higher risk of adverse cardiovascular outcomes, including all-cause death, myocardial infarction, stroke, or coronary revascularization, among patients with ASCVD. These findings remained consistent even after adjusting for lipid-lowering strategies and mean LDL-C levels.

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