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Visit-to-Visit Low-Density Lipoprotein Cholesterol Variability and Risk of Cardiovascular Outcomes

Insights From the TNT Trial

Sripal Bangalore, MD, MHA,* Andrei Breazna, PhD,† David A. DeMicco, PharmD,† Chuan-Chuan Wun, PhD,† Franz H. Messerli, MD,‡ on behalf of the TNT Steering Committee and Investigators

ABSTRACT

BACKGROUND Studies demonstrate that lowering low-density lipoprotein cholesterol (LDL-C) using a statin is associated with significant reduction in cardiovascular events. Whether visit-to-visit variability in LDL-C levels affects cardiovascular outcomes is unknown.

OBJECTIVES This study sought to evaluate the role of visit-to-visit variability in LDL-C levels on cardiovascular outcomes.

METHODS We evaluated patients with coronary artery disease and LDL-C <130 mg/dl enrolled in the TNT (Treating to New Targets) trial, randomly assigned to receive atorvastatin 80 mg/day versus 10 mg/day and with at least one post-baseline measurement of LDL-C. Visit-to-visit LDL-C variability was evaluated from 3 months into random assignment through the use of various measurements of LDL-C variability: SD, average successive variability (ASV), coefficient of variation, and variation independent of mean, with the first 2 measurements used as the primary measurements. Primary outcome was any coronary event, and secondary outcomes were any cardiovascular event, death, myocardial infarction, or stroke.

RESULTS Among 9,572 patients, SD and ASV were significantly lower with atorvastatin 80 mg/day versus 10 mg/day (SD: 12.03 ± 9.70 vs. 12.52 ± 7.43; $p = 0.005$; ASV: 12.84 ± 10.48 vs. 13.76 ± 8.69; $p < 0.0001$). In the adjusted model, each 1-SD increase in LDL-C variability (by ASV) increased the risk of any coronary event by 16% (hazard ratio [HR]: 1.16; 95% confidence interval [CI]: 1.10 to 1.23; $p < 0.0001$), any cardiovascular event by 11% (HR: 1.11; 95% CI: 1.07 to 1.15; $p < 0.0001$), death by 23% (HR: 1.23; 95% CI: 1.14 to 1.34; $p < 0.0001$), myocardial infarction by 10% (HR: 1.10; 95% CI: 1.02 to 1.19; $p = 0.02$), and stroke by 17% (HR: 1.17; 95% CI: 1.04 to 1.31; $p = 0.01$), independent of treatment effect and achieved LDL-C levels. Results were largely consistent when adjusted for medication adherence.

CONCLUSIONS In subjects with coronary artery disease, visit-to-visit LDL-C variability is an independent predictor of cardiovascular events. (J Am Coll Cardiol 2015;65:1539–48) © 2015 by the American College of Cardiology Foundation.

Data from multiple randomized trials and meta-analyses have demonstrated a significant and consistent reduction in the risk of cardiovascular events with statins that parallel low-density lipoprotein cholesterol (LDL-C) lowering, with greater benefit in a higher-risk subgroup of patients (those with known coronary artery disease [CAD]) (1–4). This has been shown for both secondary prevention (2) and for primary prevention (5,6). Consequently, major national and international

From the *Division of Cardiology, New York University School of Medicine, New York, New York; †Pfizer, New York, New York; and the ‡Division of Cardiology, St. Luke's-Roosevelt Hospital, Mount Sinai School of Medicine, New York, New York. The TNT study was sponsored by Pfizer Inc. Dr. Bangalore has been an ad-hoc consultant to Daiichi-Sankyo, Pfizer, and Boehringer Ingelheim. Drs. Breazna, Wun, and DeMicco are employees of Pfizer. Dr. Messerli has been an ad-hoc consultant to Abbott, Novartis, Pfizer, Bayer, Forest, Takeda, and Daiichi-Sankyo; and he has received research grants from Novartis and Boehringer Ingelheim. This work was presented in part at the 2012 Annual Scientific Session of the European Society of Cardiology, Munich, Germany.

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ABBREVIATIONS AND ACRONYMS

ASV = average successive variability

CAD = coronary artery disease

CV = coefficient of variation

HR = hazard ratio

LDL-C = low-density lipoprotein cholesterol

MI = myocardial infarction

VIM = variation independent of mean

guidelines have strongly recommended statin therapy for patients at risk of cardiovascular events and in patients after a coronary event (7,8). In addition, a significant reduction in major vascular events has been shown with more intensive statin therapy when compared with less intensive statin therapy (1,2). In the TNT (Treating to New Targets) trial, intensive statin therapy with atorvastatin 80 mg/day reduced major cardiovascular events by 22% when compared with standard statin therapy with atorvastatin 10 mg/day (2). Although intensive statin therapy reduced the risk of cardiovascular events in TNT, there still remains a residual risk of cardiovascular events in the intensive statin therapy group.

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Visit-to-visit variability in blood pressure has been shown to predict the risk of adverse long-term cardiovascular outcomes including stroke in patients with hypertension, independent of achieved systolic pressure. This suggests a preference for more uniform/less variable blood pressure, despite the natural diurnal variation in blood pressure (9–11). Although statin therapy lowers LDL-C, variability in LDL-C levels is not uncommon. Whether visit-to-visit variability in LDL-C affects future cardiovascular outcomes is not known. Moreover, the question is increasingly important for patients receiving intermittent statin therapy, patients who are noncompliant with therapy, and for trials with monoclonal antibodies to PCSK-9, because the LDL-C variability appears to be less with every 2-week dosing compared with every 4-week dosing with these agents (12). Our objective was to evaluate the relationship between visit-to-visit variability in LDL-C and risk of coronary and other cardiovascular events through the use of data from the TNT trial.

METHODS

PATIENT POPULATION. This is a post-hoc analysis from the TNT trial which was a double-blind, parallel-group study in patients 35 to 75 years of age who had known CAD (defined by one or more of the following: previous myocardial infarction [MI], previous or current angina with objective evidence of CAD, or prior coronary revascularization), with an LDL-C level <130 mg/dl. Patients were randomly assigned 1:1 to atorvastatin 80 mg/day versus 10 mg/day. The design and the principal results have been described in detail previously (2,13). The TNT trial is registered on clinicaltrials.gov (NCT00327691). The institutional review board at each participating site approved the trial, and written informed consent was obtained from each patient.

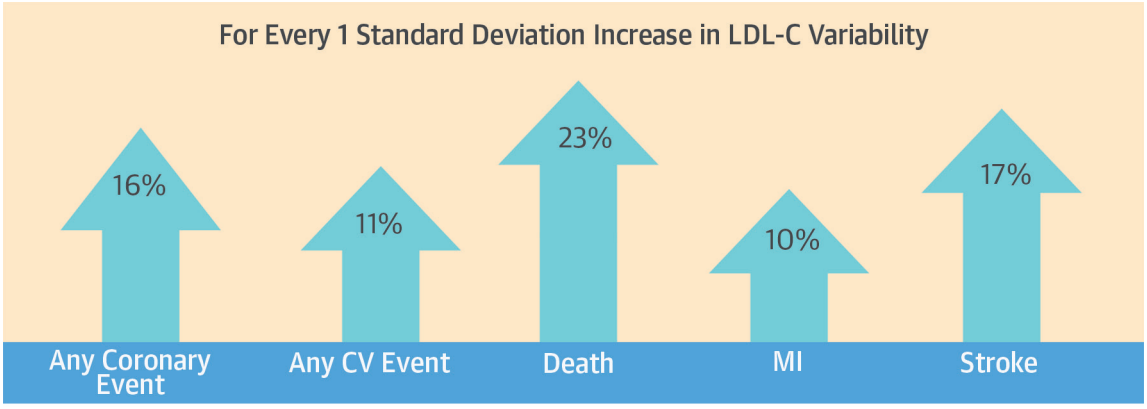
LDL-C VARIABILITY MEASUREMENTS. For this analysis, subjects with at least 1 post-baseline LDL-C measurements were included. Visit-to-visit variability in achieved LDL-C levels was evaluated through the use of LDL-C measurements from 3 months onward into random assignment because this was the period in which the LDL-C levels in the 2 treatment arms were relatively stable after the initial decrease. Visit-to-visit LDL-C variability was defined as variability in LDL-C values between visits. For patients with missing LDL-C values at any visit, any other available LDL-C data were used to calculate LDL-C variability. Various measurements of variability were used: 1) the SD of LDL-C levels; 2) the average successive variability (ASV), which was defined as the average absolute difference between successive values; 3) coefficient of variation (CV); and 4) variability independent of the mean (VIM). VIM was calculated as $100 \times \mathrm{SD}/\mathrm{Mean}^{\mathrm{beta}}$, where beta is the regression coefficient, on the basis of natural logarithm of SD on natural logarithm of mean. In addition, this uncorrected VIM was corrected by use of the formula [VIM uncorrected $\times$ (mean of CV)]/(mean of VIM uncorrected). In the TNT trial, the achieved mean LDL-C was significantly lower in the atorvastatin 80 mg/day when compared with atorvastatin 10 mg/day, and, because of this variability, measurements that are less sensitive to mean LDL-C levels such as SD and ASV were used as the primary analysis and were preferentially used for data interpretation and inference, although all 4 measurements are presented.

FOLLOW-UP. Patients were followed up at week 12 and at months 6, 9, and 12 during the first year and then every 6 months thereafter. At each visit, vital signs, clinical endpoints, adverse events, and concurrent medication information were recorded. In addition, on alternating visits (i.e., annually), physical examinations and electrocardiograms were performed and laboratory specimens, including LDL-C cholesterol measurements, were collected.

STUDY OUTCOMES. The primary outcome for this analysis was the occurrence of any coronary event defined as coronary heart disease death, non-fatal MI, resuscitated cardiac arrest, revascularization or angina. The secondary outcomes were any cardiovascular event (any coronary event or cerebrovascular event, peripheral vascular disease, heart failure), death, MI, or stroke (2).

STATISTICAL ANALYSIS. The Cox proportional hazards regression model was used to evaluate the

CENTRAL ILLUSTRATION **Visit-to-Visit LDL-C Variability and Outcomes**



Bangalore, S. et al. J Am Coll Cardiol. 2015; 65(15):1539–48.

Visit-to-visit LDL-C variability was defined as variability in LDL-C values between visits, on the basis of 9,572 patients from the TNT trial. LDL-C variability measured from 3 months onward into random assignment because this was the relatively steady phase in LDL-C after the initial decrease. CV = cardiovascular; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction.

relationship between LDL-C variability measurements and the risk of primary and secondary outcomes for the overall cohort. Three different models were used to calculate the hazard ratio (HR) for primary and secondary outcomes per 1-SD increase of variability in LDL-C: model 1 was the unadjusted model with LDL-C variability used as a continuous variable; model 2 adjusted model 1 for treatment effect (atorvastatin 80 mg/day vs. 10 mg/day); and model 3 adjusted model 2 to mean LDL-C values (continuous). Analyses were also performed to evaluate the above relationship for the 2 randomized groups separately, and the interaction between treatment and LDL-C variability parameter groups was on the basis of the Wald test of the interaction from a Cox proportional hazards model including treatment, LDL-C variability parameter, and the corresponding interaction term in the model. All analyses were performed with the use of SAS software version 9.0 (SAS Institute, Cary, North Carolina). A value of $p < 0.05$ (2-sided) was considered statistically significant.

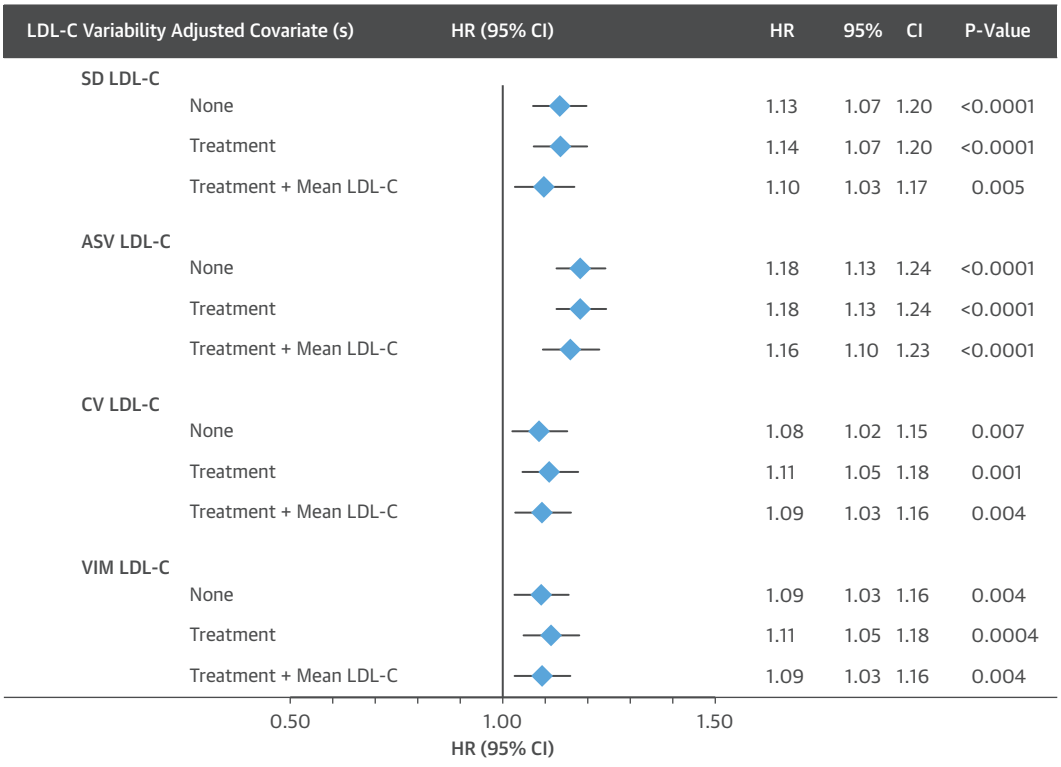
SENSITIVITY ANALYSES. A number of analyses were performed to assess the robustness of the findings: 1) adjustment for medication adherence: because LDL-C levels can be heavily influenced by patient medication adherence, we performed additional analyses adjusting for medication adherence (using pill count) as a time-dependent covariate; 2) restricting the cohort to those with non-missing LDL-C values at every visit; 3) use of LDL-C variability measurement as a time-dependent covariate to assess if the risk varied with time; and 4) assessment of interaction between baseline variables and LDL-C variability measurement and outcomes.

RESULTS

Among the 10,001 patients included in the TNT trial, 9,572 patients with at least 1 post-baseline lipid measurement were included in this analysis. Atorvastatin 80 mg/day was associated with significant reduction in mean LDL-C (-23.7; 95% CI: -24.4 to -23; $p < 0.0001$) minimum LDL-C (-22.2; 95% CI: -22.9 to -21.5; $p < 0.0001$), and maximum LDL-C (-23.7; 95% CI: -24.7 to -22.7; $p < 0.0001$] when compared with atorvastatin 10 mg/day. In addition, atorvastatin 80 mg/day was associated with lower visit-to-visit LDL-C variability (SD: 12.03 ± 9.70 vs. 12.52 ± 7.43; $p = 0.005$; ASV: 12.84 ± 10.48 vs. 13.76 ± 8.69; $p < 0.0001$) when compared with atorvastatin 10 mg/day.

VISIT-TO-VISIT LDL-C VARIABILITY AND ANY CORONARY EVENT. In the unadjusted model, visit-to-visit LDL-C variability was associated with a significant increase in the risk of any coronary event (Figure 1). For every 1-SD increase in LDL-C, the risk of any coronary event increased by 13% (HR: 1.13; 95% CI: 1.07 to 1.20; $p < 0.0001$). In addition, visit-to-visit LDL-C as measured by SD LDL-C was an independent predictor of any coronary event even after controlling

FIGURE 1 LDL-C Variability Measurements and the Risk of Any Coronary Event



For every 1-SD increase in LDL-C variability, the risk of any coronary event increased in the unadjusted model and models adjusted for treatment and adjusted for treatment and mean LDL-C levels. ASV = average successive variability; CI = confidence interval; CV = coefficient of variation; HR = hazard ratio; LDL-C = low-density lipoprotein cholesterol; VIM = variation independent of mean.

for randomized treatment group and mean achieved LDL-C levels. A similar relationship was seen with ASV of LDL-C and also with other measurements of LDL-C variability and the risk of any coronary event.

Analyses were performed to evaluate the independent effect of randomized treatment, LDL-C values, and visit-to-visit LDL-C variability measurements (Table 1). When LDL-C variables (mean, minimum, or maximum) were added to treatment variable, the HR for treatment effect was no longer significant, indicating that the treatment effect is mediated through reducing the mean, minimum, or maximum LDL-C levels. However, the treatment effect stayed significant after adjusting for LDL-C variability measurements, indicating that the impact of visit-to-visit LDL-C variability and treatment effect on any coronary event are independent (Table 1).

VISIT-TO-VISIT LDL-C VARIABILITY AND ANY CARDIOVASCULAR EVENT. In the unadjusted model, visit-to-visit LDL-C variability was associated with significant increase in the risk of any cardiovascular event (Figure 2). For every 1-SD increase in LDL-C, the risk of any cardiovascular event increased by 8% (HR: 1.08; 95% CI: 1.04 to 1.12; $p < 0.0001$). In addition, visit-to-visit LDL-C as measured by SD LDL-C was an independent predictor of any cardiovascular event even after controlling for randomized treatment and mean achieved LDL-C levels. A similar relationship was seen with ASV of LDL-C and also with other measurements of LDL-C variability and the risk of any cardiovascular event.

When LDL-C variables (mean, minimum, or maximum) were added to treatment variable, the HR for treatment effect was no longer significant, indicating that the treatment effect is mediated through reducing the mean, minimum, or maximum LDL-C levels (Table 2). However, the treatment effect stayed significant after adjusting for LDL-C variability measurements, indicating that the impact of visit-to-visit LDL-C variability and treatment effect on any cardiovascular event are independent (Table 2).

VISIT-TO-VISIT LDL-C VARIABILITY AND DEATH. Every 1 SD of ASV of LDL-C was associated with a 17% increase in death (HR: 1.17; 95% CI: 1.08 to 1.25;

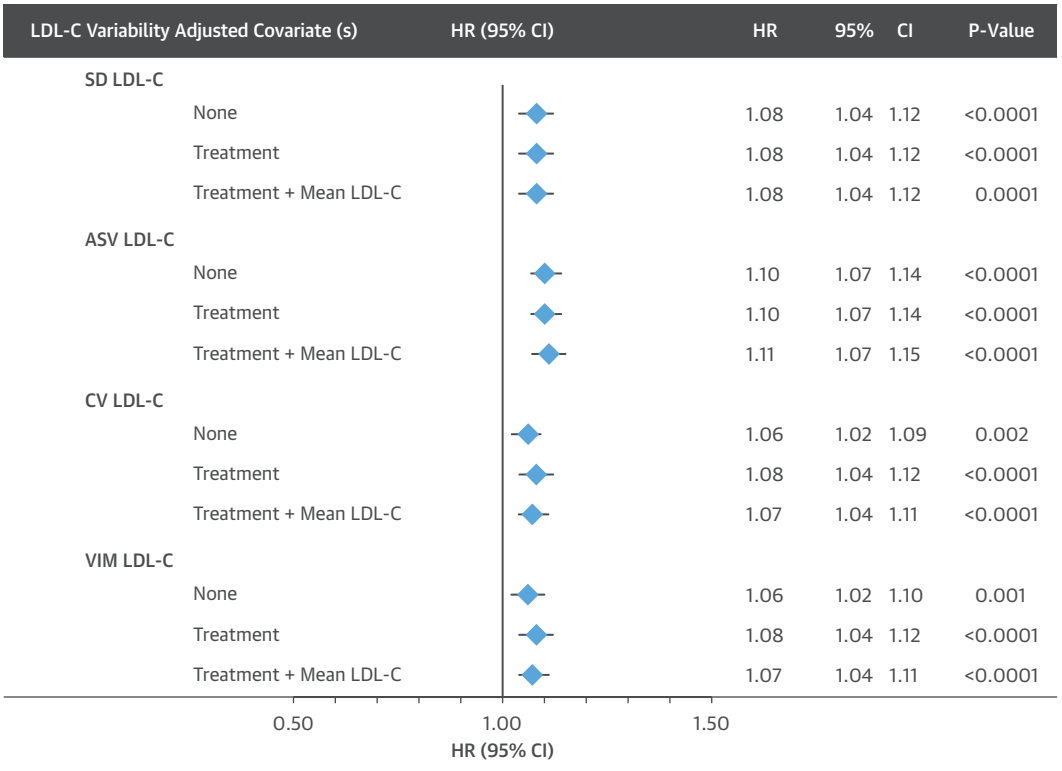
TABLE 1 Effects of Randomized Treatment Allocation on the Risk of Any Coronary Events Adjusted for Parameters of LDL-C (as a Continuous Variable)

	HR for Treatment Effect		HR for 1-SD Increase in Mean LDL-C		HR for 1-SD Increase in LDL-C Variability	
Independent Variables	**HR (95% CI)**	**p Value**	**HR (95% CI)**	**p Value**	**HR (95% CI)**	**p Value**
Treatment (Rx)	0.80 (0.70–0.91)	0.001	–	–	–	–
LDL-C					–	–
Rx + mean LDL-C	0.95 (0.81–1.10)	0.47	1.16 (1.08–1.25)	<0.0001	–	–
Rx + minimum LDL-C	0.92 (0.79–1.07)	0.29	1.13 (1.05–1.22)	0.002	–	–
Rx + maximum LDL-C	0.88 (0.76–1.00)	0.06	1.12 (1.05–1.19)	0.001	–	–
LDL-C variability						
Rx + SD LDL-C	0.80 (0.70–0.91)	0.001	–	–	1.13 (1.07–1.20)	<0.0001
Rx + ASV LDL-C	0.81 (0.71–0.92)	0.001	–	–	1.18 (1.13–1.24)	<0.0001
Rx + CV LDL-C	0.77 (0.67–0.88)	<0.0001	–	–	1.11 (1.04–1.18)	0.001
Rx + VIM LDL-C	0.77 (0.68–0.88)	<0.0001	–	–	1.11 (1.05–1.18)	0.0004
Rx + mean LDL-C + SD LDL-C	0.89 (0.76–1.04)	0.14	1.10 (1.01–1.20)	0.02	1.10 (1.03–1.17)	0.005
Rx + mean LDL-C + ASV LDL-C	0.86 (0.74–1.01)	0.06	1.06 (0.98–1.16)	0.13	1.16 (1.09–1.23)	<0.0001
Rx + mean LDL-C + CV LDL-C	0.90 (0.77–1.05)	0.17	1.14 (1.06–1.23)	0.0004	1.09 (1.03–1.16)	0.004
Rx + mean LDL-C + VIM LDL-C	0.90 (0.77–1.05)	0.17	1.14 (1.06–1.23)	0.001	1.09 (1.03–1.16)	0.004

Values are HR and 95% confidence intervals and their corresponding p Values.

ASV = average successive variability; CI = confidence interval; CV = coefficient of variation; HR = hazard ratio; LDL-C = low-density lipoprotein cholesterol; VIM = variation independent of mean.

FIGURE 2 LDL-C Variability Measurements and the Risk of Any Cardiovascular Event



For every 1-SD increase in LDL-C variability, the risk of any cardiovascular event increased in the unadjusted model and models adjusted for treatment and adjusted for treatment and mean LDL-C levels. Abbreviations as in Figure 1.

TABLE 2 Effects of Randomized Treatment Allocation on the Risk of Any Cardiovascular Events Adjusted for Parameters of LDL-C (as a Continuous Variable)

	HR for Treatment Effect		HR for 1-SD Increase in Mean LDL-C		HR for 1-SD Increase in LDL-C Variability	
Independent Variables	**HR (95% CI)**	**p Value**	**HR (95% CI)**	**p Value**	**HR (95% CI)**	**p Value**
Treatment (Rx)	0.77 (0.60–0.98)	0.04	–	–	–	–
LDL-C						
Rx + mean LDL-C	0.75 (0.56–1.01)	0.06	0.98 (0.85–1.14)	0.81	–	–
Rx + minimum LDL-C	0.77 (0.57–1.04)	0.09	1.00 (0.86–1.16)	0.98	–	–
Rx + maximum LDL-C	0.79 (0.60–1.03)	0.08	1.03 (0.90–1.17)	0.69	–	–
LDL-C variability						
Rx + SD LDL-C	0.77 (0.60–0.99)	0.04	–	–	1.10 (0.99–1.23)	0.08
Rx + ASV LDL-C	0.78 (0.61–0.99)	0.04	–	–	1.13 (1.02–1.25)	0.02
Rx + CV LDL-C	0.74 (0.58–0.95)	0.02	–	–	1.10 (0.98–1.24)	0.10
Rx + VIM LDL-C	0.74 (0.58–0.95)	0.02	–	–	1.10 (0.98–1.24)	0.09
Rx + mean LDL-C + SD LDL-C	0.70 (0.52–0.95)	0.02	0.91 (0.78–1.08)	0.29	1.14 (1.00–1.29)	0.04
Rx + mean LDL-C + ASV LDL-C	0.70 (0.51–0.94)	0.02	0.90 (0.77–1.06)	0.22	1.17 (1.04–1.31)	0.01
Rx + mean LDL-C + CV LDL-C	0.71 (0.53–0.97)	0.03	0.97 (0.83–1.12)	0.67	1.11 (0.98–1.24)	0.09
Rx + mean LDL-C + VIM LDL-C	0.71 (0.53–0.97)	0.03	0.96 (0.83–1.12)	0.63	1.11 (0.99–1.24)	0.08

Values are HR and 95% confidence intervals and their corresponding p Values.
Abbreviations as in Table 1.

$p < 0.0001$) in an unadjusted model and a 23% increase in death-independent-of-treatment effect and achieved LDL-C levels in the adjusted model. Results were similar for SD of LDL-C, although this did not reach statistical significance (adjusted HR: 1.06; 95% CI: 0.96–1.17; $p = 0.23$).

VISIT-TO-VISIT LDL-C VARIABILITY AND MYOCARDIAL INFARCTION. Every 1 SD of ASV of LDL-C was associated with a 14% increase in MI (HR: 1.14; 95% CI: 1.06 to 1.23; $p = 0.0002$) in the unadjusted model (**Figure 3**) and a 10% increase in MI independent of treatment effect and achieved LDL-C levels (**Figure 3**) in the adjusted model. Results were similar for SD of LDL-C, although this did not reach statistical significance (adjusted HR: 1.07; 95% CI: 0.98 to 1.17; $p = 0.13$).

VISIT-TO-VISIT LDL-C VARIABILITY AND STROKE. Every 1 SD of ASV of LDL-C was associated with a 13% increase in stroke (HR: 1.13; 95% CI: 1.02 to 1.25; $p = 0.02$) in the unadjusted model (**Figure 4**) and a 17% increase in stroke independent of treatment effect and achieved LDL-C levels (**Figure 3**) in the adjusted model. Results were similar for SD of LDL-C (adjusted HR: 1.14; 95% CI: 1.01 to 1.29; $p = 0.04$).

There was no significant interaction between LDL-C variability measurements and treatment effect for the above clinical outcomes, such that the relationship was similar for atorvastatin 10 mg/day versus 80 mg/day groups (Online Tables 1 to 4).

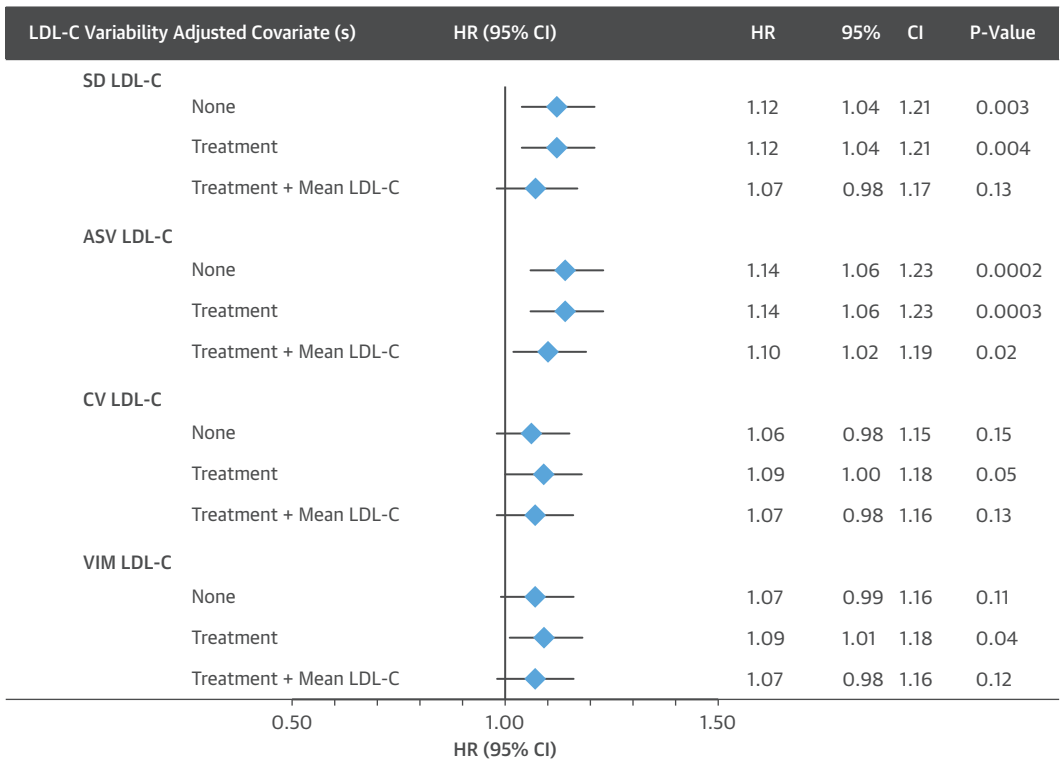
SENSITIVITY ANALYSES. The results were similar in a sensitivity analysis adjusting for treatment adherence (included as a time-dependent covariate) (Online Table 5). Every 1-SD increase of ASV of LDL-C was associated with a 17% increase in any coronary event, 10% increase in any cardiovascular event, 13% increase in non-fatal MI, and 13% increase in stroke (Online Table 5), even after controlling for medication adherence. Similarly, the results were largely consistent in the sensitivity analyses restricted to the cohort without missing LDL-C values at any scheduled visit (Online Table 6) and in the analyses that used LDL-C variability as a time-dependent covariate (Online Table 7). The test for interaction of select baseline characteristics was largely non-significant (except for hypertension and the outcome of stroke) (Online Table 8).

DISCUSSION

The results of this study indicate that visit-to-visit LDL-C variability is a powerful and independent predictor of any coronary event, any cardiovascular event, death, MI, and stroke, independent of treatment effect and achieved LDL-C levels (**Central Illustration**). In the adjusted model, each 1-SD increase in LDL-C variability (as measured by ASV) increased the risk of any coronary event by 16%, any cardiovascular event by 11%, death by 23%, MI by 10%, and stroke by 17%, independent of statin dose and achieved LDL-C levels. The association was significant even after controlling for treatment adherence.

STATINS AND CARDIOVASCULAR OUTCOMES. Randomized trials, observational studies, and meta-analyses

FIGURE 3 **LDL-C Variability Measurements and the Risk of MI**

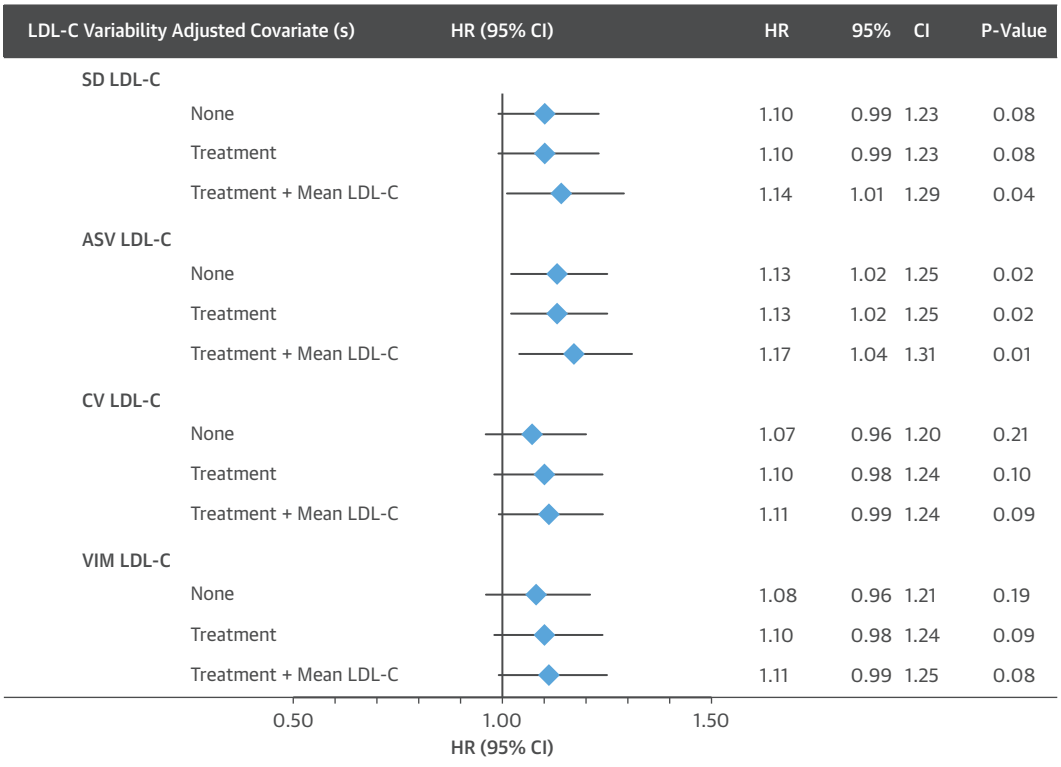


For every 1-SD increase in LDL-C variability, the risk of MI increased in the unadjusted model and models adjusted for treatment and adjusted for treatment and mean LDL-C levels. Abbreviations as in Figure 1.

have shown a significant benefit of statins for primary prevention of cardiovascular events as well as for secondary prevention (1–4). The results from these studies indicate that lowering of LDL-C by 1 mmol/l (approximately 39 mg/dl) with a statin reduces the incidence of major vascular events by approximately 20% (4). The standard statin regimen reduces LDL-C by approximately 30%, with more intensive statin regiment reducing this level by approximately 50% (4). In addition to a reduction in LDL-C, other pleotropic effects such as anti-inflammatory properties, plaque stabilization, and others appear to contribute to the significant benefit of statin therapy. It is therefore not surprising that statins are the mainstay for prevention and treatment of patients with CAD and are endorsed by major national and international guidelines (7,8). Despite this, there remains a residual risk of cardiovascular events even in patients receiving an intensive statin regimen. In the TNT trial, although intensive statin treatment with atorvastatin 80 mg/day reduced cardiovascular events when compared with atorvastatin 10 mg/day, the residual risk of major cardiovascular events was 8.7%, death was 5.7%, MI was 4.9%, and stroke was 2.3% (2).

Visit-to-visit variability in blood pressure is an independent predictor of adverse cardiovascular events, which suggests that a more uniform/less variable blood pressure is desirable (10). This is true despite that fact that there is variability in blood pressure measurement with time of day and with stress, activity, and emotions. However, it is not known if the same is applicable to LDL-C control. In the present study, we measured variability in the LDL-C levels from 3 months after the initial decrease onward into random assignment because this was the period in which the LDL-C levels in the 2 treatment arms were relatively stable. The results of the present study indicate a strong and independent effect of visit-to-visit variability measurements on long-term cardiovascular outcomes. Each 1-SD increase in visit-to-visit variability in LDL-C was associated with a significant increase in any coronary event, any cardiovascular event, death, MI, and stroke, and this was independent of treatment effect and achieved LDL-C levels, which suggests that a more uniform and

FIGURE 4 LDL-C Variability Measurements and the Risk of Stroke



For every 1-SD increase in LDL-C variability, the risk of stroke increased in the unadjusted model and models adjusted for treatment and adjusted for treatment and mean LDL-C levels. Abbreviations as in Figure 1.

less variable visit-to-visit LDL-C is important. The results of the present study also indicate that visit-to-visit variability in LDL-C was lower with atorvastatin 80 mg/day when compared with atorvastatin 10 mg/day. It therefore lends credence to the American College of Cardiology/American Heart Association blood cholesterol guideline recommendation of moderate- to high-intensity statins in patients with atherothrombotic vascular disease (7), not only for a more robust reduction in LDL-C but also for less variability in LDL-C. Although the dose of statin was predictive of visit-to-visit LDL-C variability, other factors such as adherence with medication also play a role. In an analysis of 782 patients, visit-to-visit variability in LDL-C was strongly associated with statin non-adherence (odds ratio: 3.4; 95% CI: 1.7 to 7.1) (14). However, in our analyses, LDL-C variability was an independent predictor of events even after controlling for statin non-adherence. In addition, visit-to-visit LDL-C variability may be important in patients receiving intermittent statin therapy. Alternative dosing schedules such as a few times per week, every other day, or even once per week have been investigated as methods to reduce myalgias and yet achieve efficacy in lowering LDL-C. Intermittent statin therapy, especially with longer-acting agents such as rosuvastatin or atorvastatin, is used in patients who are intolerant to daily statin therapy and has been shown to result in significant LDL-C reduction, although variability was not reported in these retrospective studies (15–18). The Canadian Working Group has recommended intermittent therapy for suspected statin intolerance (19). However, it remains unknown whether intermittent statin dosage provides the same cardiovascular protection as does daily statin therapy (18). The results of the present study are interesting with regard to monoclonal antibodies to PCSK-9 because the visit-to-visit variability with a once-per-month injection could be substantial. In the LAPLACE-TIMI 57 trial (LDL-C Assessment With PCSK9 monoclonaL Antibody Inhibition Combined With Statin therapy-Thrombolysis In Myocardial Infarction 57), the LDL-C variability was less when the medication was dosed every 2 weeks rather than

every 4 weeks (12). However, whether it affects clinical outcomes must be tested in future trials.

LDL-C VARIABILITY AND ADVERSE OUTCOMES. The mechanism linking increased LDL-C variability to an increased risk of cardiovascular events is unknown, but there are several hypotheses. Statins stabilize plaque mainly (but not exclusively) by a cholesterol-dependent mechanism, reducing the cholesterol content of plaque. Lipid lowering in turn inhibits inflammation and decreases collagenolytic activity and thrombotic potential. In addition, the cholesterol-independent action of statins through alterations in the function of G proteins also contributes to their anti-inflammatory and antithrombotic actions. LDL-C variability may cause instability at the vascular wall as a result of variability in lipid efflux mechanism (i.e., impair the cholesterol-dependent mechanism of plaque stabilization) and thus increase the potential for plaque vulnerability and rupture, thereby increasing the risk of cardiovascular events. Another potential mechanism of this increased risk is perhaps that LDL-C variability is an epiphenomenon of other systemic conditions that increase cardiovascular risk. It is possible that patients with systemic conditions leading to generalized frailty might have higher variability of multiple biological parameters and increased risk caused by several pathologic mechanisms. Finally, poor adherence to medications may link LDL variability with increased risk of cardiovascular events. LDL variability was an independent predictor of events even after controlling for medication adherence. However, adherence was measured by means of pill counts without testing the "taking compliance" (i.e., whether a medication was actually taken) by use of drug levels. Further studies are needed to test this hypothesis.

STUDY LIMITATIONS. Our data are derived from a randomized trial in which the visit-to-visit LDL-C variability probably is less than in real-world patients. Despite this, LDL-C variability measurements were strong and independent predictors of cardiovascular events. We did not have data on other factors that could result in higher LDL-C variability, including contents and proximity to the last meal. However, all lipid parameters in the TNT trial were measured in a fasting state, thus reducing the variability caused by proximity of the last meal. In addition, the results were not consistently seen across all measurements of LDL-C variability, but the results were largely similar. Moreover, variability measurements that are less sensitive to mean LDL levels such as SD and ASV produced largely consistent results.

CONCLUSIONS

In patients enrolled in the TNT trial, visit-to-visit variability in LDL-C was a strong and independent predictor of cardiovascular events independent of treatment effect, achieved LDL-C levels, and statin adherence. A 1-SD increase in LDL-C variability increased the risk of any coronary event by 16%, any cardiovascular event by 11%, death by 23%, MI by 10%, and stroke by 17% (**Central Illustration**). Although yet to be confirmed in future studies, our results are important, given the increased variability in LDL-C in recent clinical trials that used monoclonal antibodies to PCSK-9 with every 4-weeks dosing versus every 2-weeks dosing (12) and with intermittent statin dosing strategies (19).

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Sripal Bangalore, Cardiac Catheterization Laboratory, The Leon H. Charney Division of Cardiology, New York University School of Medicine, 550 First Avenue, New York, New York 10016. E-mail: sripalbangalore@gmail.com.

PERSPECTIVES

COMPETENCY IN PATIENT CARE: Greater variability of serum LDL-C levels between visits is associated with adverse clinical cardiovascular outcomes.

TRANSLATIONAL OUTLOOK: Further research is needed to evaluate predictors of variability in serum LDL-C levels and identify interventions that ameliorate these adverse effects.

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APPENDIX For supplemental tables, please see the online version of this article.