Visit-to-visit variability of lipid measurements as predictors of cardiovascular events Presented in part at the American Heart Association Annual Scientific Sessions, November 2017.

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BACKGROUND: Higher visit-to-visit variability in risk factors such as blood pressure and low-density lipoprotein (LDL)-cholesterol are associated with an increase in cardiovascular (CV) events.

OBJECTIVE: The purpose of this study was to determine whether variability in high-density lipoprotein cholesterol (HDL-C) and triglyceride levels predicted coronary and CV events in a clinical trial population with known coronary disease.

METHODS: We assessed intraindividual variability in fasting high-density lipoprotein (HDL)-cholesterol, triglyceride, and LDL-cholesterol measurements among 9572 patients in the Treating to New Targets trial and correlated the results with coronary events over a median follow-up of 4.9 years.

RESULTS: In the fully adjusted Cox model, 1 standard deviation of average successive variability, defined as the average absolute difference between successive values, was associated with an increased risk of a coronary event for HDL-cholesterol (hazard ratio [HR] 1.16, 95% confidence interval [CI] 1.11–1.21, $P < .0001$), for triglycerides (HR 1.09, 95% CI 1.04–1.15, $P = .0005$), and for LDL-cholesterol (HR 1.14, 95% CI 1.09–1.19, $P < .0001$). Similar results were found for the 3 other measures of variability, standard deviation, coefficient of variability, and variability independent of the mean. Similar results were seen for CV events, stroke, and nonfatal myocardial infarction. Higher variability in triglyceride and LDL-cholesterol, but not HDL-cholesterol, was predictive of incident diabetes. The correlation among the variability of the 3 lipid measurements was weak.

CONCLUSION: Visit-to-visit variability in fasting measurements of HDL-cholesterol, triglycerides, and LDL-cholesterol are predictive of coronary events, CV events, and for triglyceride and low-density lipoprotein cholesterol variability, incident diabetes. The mechanisms accounting for these associations remain to be determined.

High levels of biological variables, including blood pressure (BP), low-density lipoprotein cholesterol (LDL-C), and body weight are associated with an increased risk of cardiovascular (CV) events, and lowering these levels has been shown to reduce CV risk. In addition, variability in these measurements is predictive of CV events; for example, long-term variability in systolic BP is associated with increased all-cause and CV mortality, as well as CV events, including coronary events and stroke.[1,2] Long-term variability of total cholesterol levels increased risk in the Framingham population,[3] and in patients with coronary disease LDL-C variability has been related to an increase in CV events.[4,5] In both Framingham and in coronary patients, variations in body weight are also associated with a higher rate of CV events.[6,7]

Although low high-density lipoprotein cholesterol (HDL-C) and high triglyceride levels are known risk factors for CV events, whether variability in HDL-C and triglyceride levels are linked to increased CV risk has not been investigated. The primary purpose of this study is to determine whether HDL-C variability and triglyceride variability predict coronary and CV events, and incident diabetes in patients in the Treating to New Targets (TNT) trial, a well-characterized population where LDL-C variability has already been related to CV events.[4] Secondary purposes include examining the correlation among LDL-C, HDL-C and triglyceride variability and assessing the relative strength of these measures of variability in predicting CV events.

Methods

Patient population

This study is a post hoc analysis of the TNT trial, where 10,001 patients aged 35 to 75 years with clinically evident coronary disease were randomly assigned to atorvastatin 10 mg or 80 mg/d and followed up for a median of 4.9 years. Inclusion criteria included an LDL-C of 130–250 mg/dL and a triglyceride level ≤600 mg/dL before treatment, and an LDL-C<130 mg/dL after an 8-week run-in period while taking atorvastatin 10 mg/d. The study design and principal results have previously been reported.[8,9] The institutional review board at each of the 256 sites approved the trial, and written informed consent was obtained from each patient. The TNT trial is registered on clinicaltrials.gov (NCT00327691).

Lipid variability measurements

Follow-up visits were scheduled at week 12 and at months 6, 9, and 12 during the first year and then every 6 months thereafter. Blood for lipids were drawn after a 12-hour fast at the week 12 visit, at 12 months, and then annually. Lipids were measured in a central laboratory using standard techniques. LDL-C was measured directly when serum triglycerides exceeded 400 mg/dL but otherwise was calculated using the Friedewald equation. Subjects with at least 2 postbaseline lipid measurements were included in this analysis. Measurements of HDL-C, triglyceride, and LDL-C levels from the 12-week visit onward were used to calculate visit-to-visit variability because lipid levels in the 2 treatment arms had stabilized by 12 weeks.

Four measurements of variability were calculated: (1) the average successive variability (ASV), defined as the average absolute difference between successive values of the available HDL-C, triglyceride, or LDL-C levels; (2) the standard deviation (SD) of successive measurements; (3) the coefficient of variation (CV); and (4) variability independent of the mean (VIM). VIM was calculated as $100 \times SD/mean^{beta}$, where beta is the regression coefficient, on the basis of natural logarithm of SD on natural logarithm of mean. This uncorrected VIM was corrected using the formula (VIM uncorrected × [mean of CV])/(mean of VIM uncorrected). The results with each of these 4 measurements of variability were relatively similar, so for the sake of simplicity, mainly ASV results are presented.

The primary outcome for this study was the occurrence of any coronary event, defined as coronary heart disease death, nonfatal myocardial infarction (MI), resuscitated cardiac arrest, revascularization, or angina. The secondary outcomes were any CV event (any coronary event or cerebrovascular event, peripheral vascular disease, hospitalization for heart failure), death, MI, stroke, or incident diabetes.

Statistical analysis

Baseline characteristics were compared between patients above and below median variability for HDL-C, triglyceride, and LDL-C variability using chi-square tests for categorical variables and 1-way analysis of variance for continuous variables. The relation between HDL-C, triglyceride, and LDL-C variability (continuous variable) and the risk of outcomes were evaluated using a Cox proportional hazards regression model. Four models were constructed (separately for HDL-C, triglycerides, and LDL-C): model 1, unadjusted model; model 2, adjusting model 1 for treatment effect (atorvastatin 80 mg vs 10 mg/d); model 3, adjusting model 2 to mean HDL-C, triglyceride, or LDL-C variability values (continuous), and model 4, where the following additional adjustments were added to model 3: age, gender, race, baseline body mass index, diabetes, hypertension, chronic kidney disease, heart failure, smoking status, LDL-C, HDL-C, total cholesterol, and triglycerides. An additional model was constructed including all the variables in model 4, plus the change in HDL-C, triglyceride, or LDL-C from week 12 to the end of follow-up. The results of this model were almost identical to model 4, and these results are thus not presented. Patients with events in the first 3 months were excluded from analysis.

For HDL-C, triglyceride, and LDL-C variability, patients were divided into quintiles of ASV, SD, CV, and VIM for the primary and secondary end points. For each of these analyses, the same adjustments were made as for the Cox proportional hazards regression model. All analyses

were performed with the use of SAS software, version 9.0 (SAS Institute, Cary, NC). A value of $P < .05$ (2 sided) was considered statistically significant.

Results

Of the 10,001 patients included in the TNT trial, 9572 had at least 2 postbaseline lipid measurements and are included in this analysis. Lipid levels were similar in the 2 treatment groups at baseline, but after 12 weeks of treatment, triglycerides were lower in the 80 mg compared to the 10 mg group (128 ± 65 mg/dL vs 152 ± 79 mg/dL) as was LDL-C (73 ± 21 mg/dL vs 99 ± 20 mg/dL). HDL-C levels at 12 weeks were similar (47 ± 11 mg/dL).

The clinical features of patients with ASV values below and above the median for HDL-C, triglycerides, and LDL-C are listed in Tables 1–3, respectively. Patients with HDL-C variability above the median were more likely to be women and to have higher HDL-C levels after 3 months of treatment. Patients with triglyceride variability above the median were younger and more likely to have diabetes compared to patients below the median. On treatment, their HDL-C levels were lower, their LDL-C levels higher, and their triglyceride levels much higher compared to patients below the median. Patients with higher LDL-C variability were more likely to be women and to have higher on-treatment LDL-C and triglyceride levels.

HDL-C variability and end point events

For each 1 SD increase in ASV of HDL-C, the risk of any coronary event increased in the unadjusted Cox model (hazard ratio [HR] 1.06, 95% confidence interval [CI] 1.02–1.10, $P = .0053$), as shown in Figure 1. Adjusting for treatment group, mean HDL-C, and clinical covariates (model 4) increased the risk (HR 1.16, 95% CI 1.11–1.21, $P < .0001$). Similar results were seen for the other measures of variability: SD, CV, and VIM, as shown in Figure 1.

Higher quintiles of ASV for HDL-C were associated with an increased risk for any coronary event, as shown in Figure 2. After adjusting for treatment group, mean HDL-C, and clinical covariates (model 4), the risk was 50% higher in quintile 5 compared to quintile 1 (HR 1.50, 95% CI 1.30–1.74, $P < .0001$). Quintile 5 included patients with an HDL-C ASV of 6.1 and higher. Similar results were seen for the other measures of variability (not shown).

Quintiles of ASV for HDL-C are also shown in Figure 2 for the broader secondary end point, any CV event, and for stroke, nonfatal MI, all-cause mortality, and new-onset diabetes. For each of these end points except new-onset diabetes, the HR was higher in quintile 5 compared to quintile 1, ranging from 1.56 to 1.81, and in each case, the trend across quintiles was highly statistically significant.

Table 1 Clinical features of patients with ASV of HDL-C above and below the median

Clinical features	ASV ≤ 4 (n = 5166)	ASV > 4 (n = 4406)	P value
Age (years)	60.7 ± 8.8	61.4 ± 8.9	.0004
Female	736 (14.3%)	1066 (24.2%)	<.0001
Caucasian	4876 (94.4%)	4144 (94.1%)	.51
Diabetes	745 (14.4%)	672 (15.3%)	.26
Hypertension	2742 (53.1%)	2421 (55.0%)	.077
Current smoker	670 (13.0%)	589 (13.4%)	.56
Previous CABG	2428 (47.0%)	2018 (45.8%)	.25
Previous PCI	2792 (54.1%)	2397 (54.4%)	.74
Heart failure	367 (7.1%)	355 (8.1%)	.081
BMI	28.8 ± 4.5	28.2 ± 4.5	<.0001
Systolic BP (mm Hg)	130.4 ± 16.8	131.0 ± 16.7	.064
Diastolic BP (mm Hg)	78.1 ± 9.3	77.8 ± 9.6	.061
On-treatment (3 mo)			
LDL-C (mg/dL)	85.0 ± 24.0	86.1 ± 24.8	.024
HDL-C (mg/dL)	43.9 ± 8.8	51.3 ± 12.4	<.0001
Triglycerides (mg/dL)	143 ± 71	136 ± 74	<.0001
CKD	1589 (30.8%)	1486 (33.7%)	.002
MDRD	65.4 ± 11.1	65.2 ± 11.6	.22
ASV HDL-C	2.71 ± 0.86	6.70 ± 3.1	<.0001
ASV LDL-C	12.2 ± 8.6	14.7 ± 10.2	<.0001
ASV triglycerides	37.3 ± 32.0	42.2 ± 44.2	<.0001

ASV, average successive variability; BMI, body mass index; BP, blood pressure; CABG, coronary artery bypass grafting; CKD, chronic kidney disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; MDRD, Modification of Diet in Renal Disease estimated glomerular filtration rate; PCI, percutaneous coronary intervention.

Table 2   Clinical features of patients with ASV of triglycerides above and below the median

Clinical features	ASV ≤ 30 (n = 4802)	ASV > 30 (n = 4770)	P value
Age (years)	62.1 ± 8.6	59.9 ± 8.9	<.0001
Female	896 (18.7%)	906 (19.0%)	.68
Caucasian	4494 (93.6%)	4526 (94.9%)	.0065
Diabetes	565 (11.8%)	852 (17.9%)	<.0001
Hypertension	2448 (51.0%)	2715 (56.9%)	<.0001
Current smoker	542 (11.3%)	717 (15.0%)	<.0001
Previous CABG	2180 (45.4%)	2266 (47.5%)	.040
Previous PCI	2540 (52.9%)	2649 (55.5%)	.0097
Heart failure	309 (6.4%)	413 (8.7%)	<.0001
BMI	27.9 ± 4.4	29.1 ± 4.6	<.0001
Systolic BP (mm Hg)	130.6 ± 17.1	130.8 ± 16.3	.67
Diastolic BP (mm Hg)	77.5 ± 9.6	78.4 ± 9.3	<.0001
On-treatment (3 mo)			
LDL-C (mg/dL)	82.4 ± 23.4	88.5 ± 24.8	<.0001
HDL-C (mg/dL)	49.3 ± 11.6	45.3 ± 10.5	<.0001
Triglycerides (mg/dL)	109 ± 42	171 ± 83	<.0001
CKD	1517 (31.6%)	1558 (32.7%)	.26
MDRD	65.5 ± 11.2	65.2 ± 11.5	.22
ASV HDL-C	4.47 ± 2.9	4.62 ± 3.0	.014
ASV LDL-C	11.6 ± 7.7	15.1 ± 10.6	<.0001
ASV triglycerides	18.6 ± 6.8	60.6 ± 44.6	<.0001

ASV, average successive variability; BMI, body mass index; BP, blood pressure; CABG, coronary artery bypass grafting; CKD, chronic kidney disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; MDRD, Modification of Diet in Renal Disease estimated glomerular filtration rate; PCI, percutaneous coronary intervention.

Table 3   Clinical features of patients with ASV of LDL-C above and below the median

Clinical features	ASV ≤ 11.12 (n = 4786)	ASV > 11.2 (n = 4786)	P value
Age (y)	61.7 ± 8.6	60.4 ± 9.0	<.0001
Female	792 (16.6%)	1010 (21.1%)	<.0001
Caucasian	4552 (95.1%)	4468 (93.4%)	.0003
Diabetes	631 (13.2%)	786 (16.4%)	<.0001
Hypertension	2514 (52.5%)	2649 (55.4%)	.0060
Current smoker	576 (12.0%)	683 (14.3%)	.0013
Previous CABG	2219 (46.4%)	2227 (46.5%)	.89
Previous PCI	2583 (54.0%)	2606 (54.5%)	.65
Heart failure	327 (6.8%)	395 (8.3%)	.0095
BMI	28.4 ± 4.4	28.7 ± 4.6	.0015
Systolic BP (mm Hg)	130.5 ± 16.7	130.9 ± 16.8	.29
Diastolic BP (mm Hg)	77.8 ± 9.4	78.2 ± 9.5	.037
On-treatment (3 mo)			
LDL-C (mg/dL)	80.2 ± 21.8	90.7 ± 25.6	<.0001
HDL-C (mg/dL)	47.3 ± 11.1	47.3 ± 11.3	.98
Triglycerides (mg/dL)	129 ± 61	151 ± 82	<.0001
CKD	1530 (32.0%)	1545 (32.3%)	.76
MDRD	65.2 ± 11.0	65.4 ± 11.6	.48
ASV HDL-C	4.15 ± 2.6	4.95 ± 3.2	<.0001
ASV LDL-C	7.3 ± 2.3	19.3 ± 10.0	<.0001
ASV triglycerides	32.1 ± 25.0	47.0 ± 46.7	<.0001

ASV, average successive variability; BMI, body mass index; BP, blood pressure; CABG, coronary artery bypass grafting; CKD, chronic kidney disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; MDRD, Modification of Diet in Renal Disease estimated glomerular filtration rate; PCI, percutaneous coronary intervention.
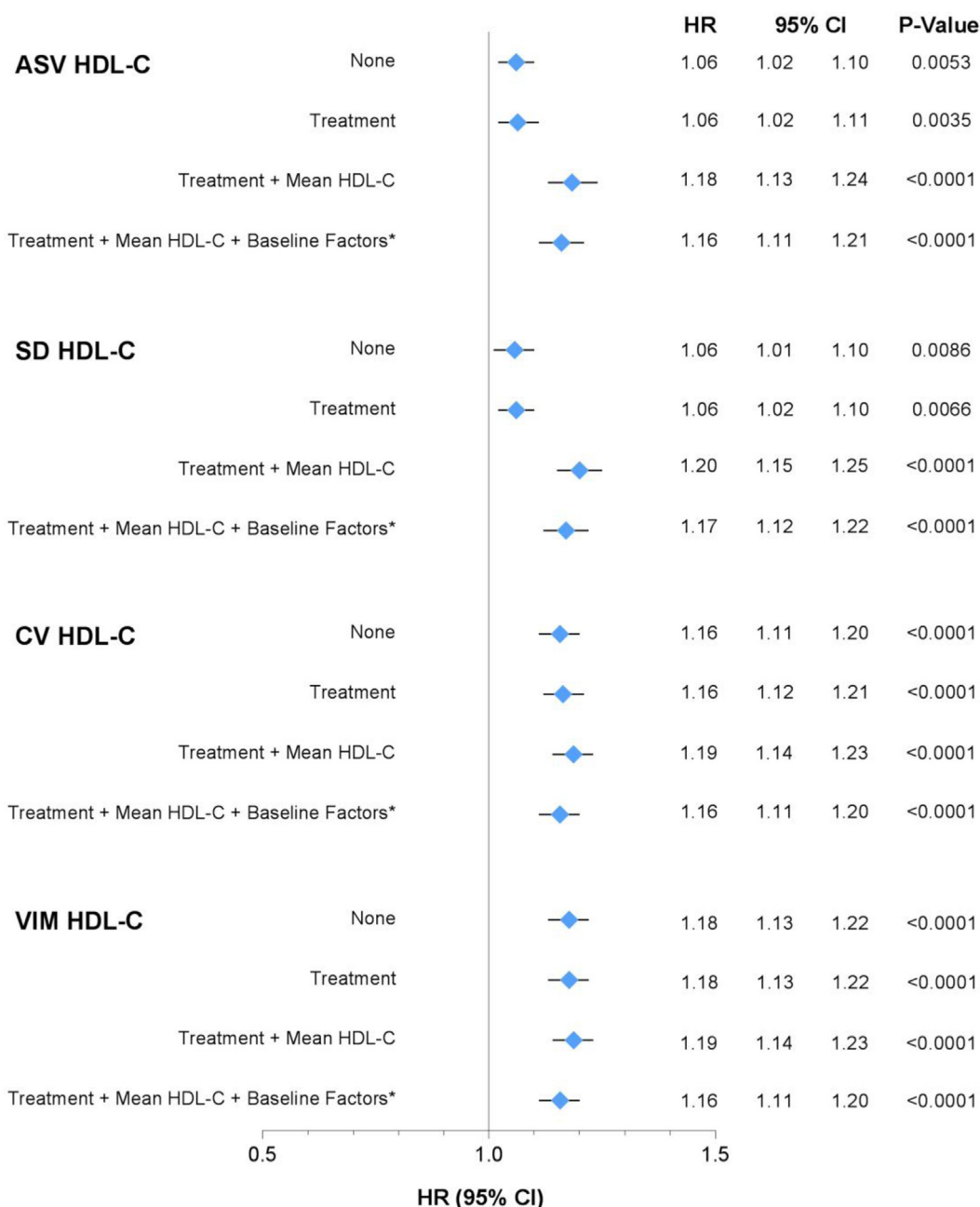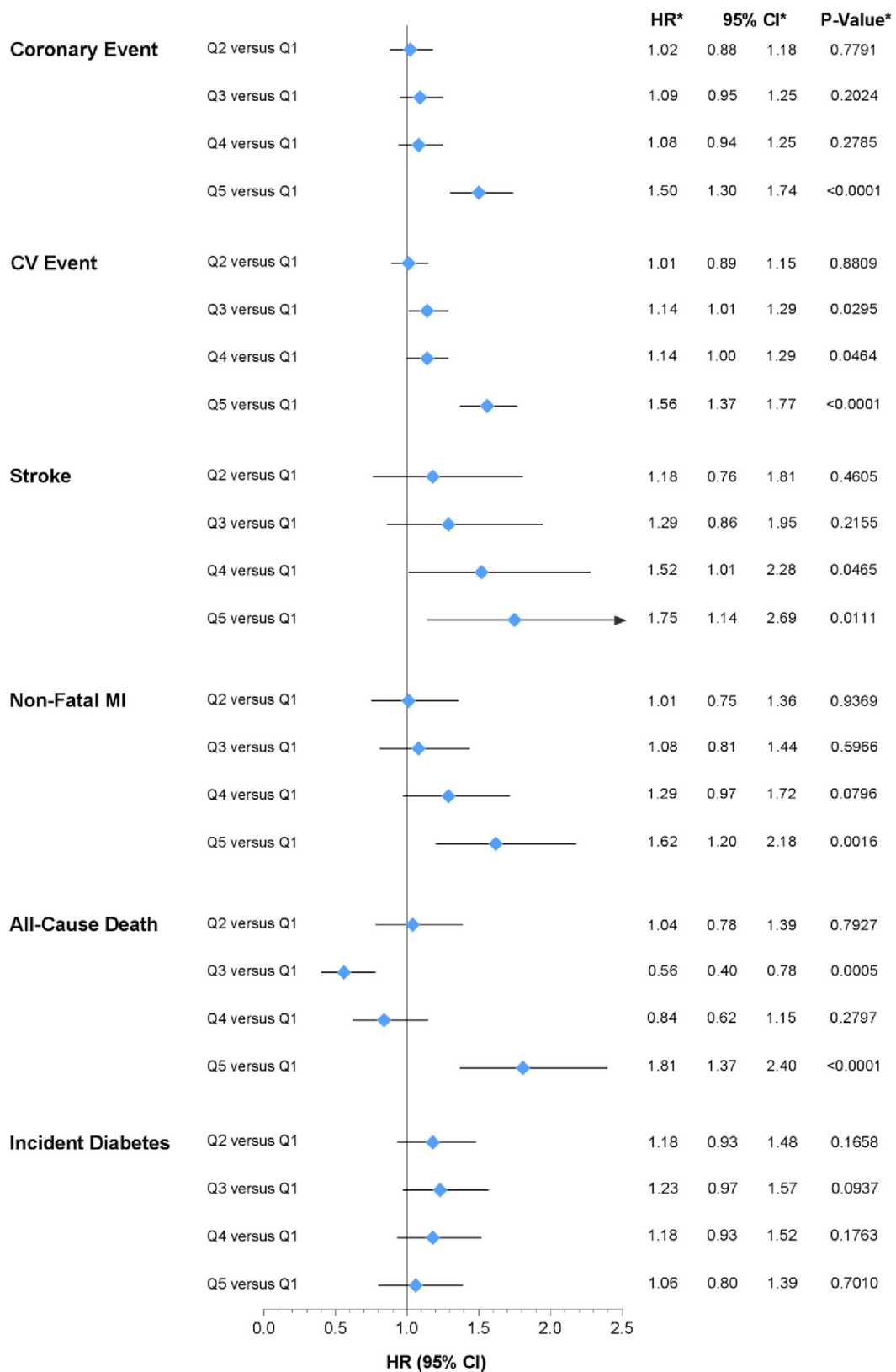
Figure 1 Risk of a coronary event in unadjusted and adjusted Cox regression models for 1 standard deviation of 4 measures of HDL-C variability: ASV, SD, CV, and VIM. *Baseline factors included age, sex, race, BMI, diabetes mellitus, hypertension, smoking status, LDL-C, HDL-C, total cholesterol, triglycerides, chronic kidney disease, and heart failure. ASV, average successive variability; CV, cardiovascular; HDL-C, high-density lipoprotein cholesterol; SD, standard deviation; VIM, variability independent of the mean.
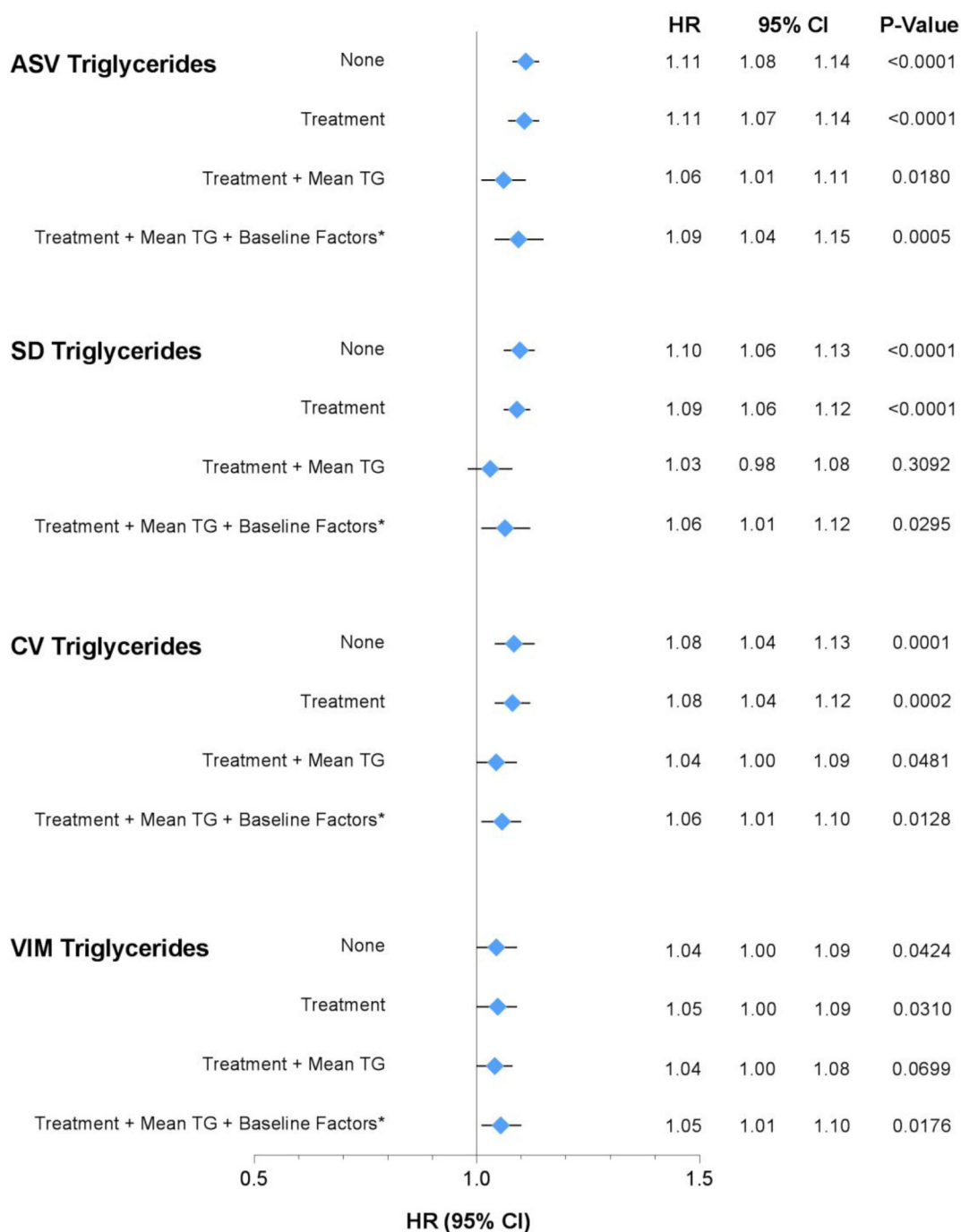
Triglyceride variability and end point events

For each 1 SD increase in ASV of triglycerides, the risk of any coronary event increased in the unadjusted Cox model (HR 1.11, 95% CI 1.08–1.14, $P < .0001$), as shown in Figure 3. Adjusting for treatment group, mean triglyceride level, and clinical covariates (model 4) slightly decreased the risk (HR 1.09, 95% CI 1.04–1.15, $P = .0005$). Similar results were seen for the other measures of variability: SD, CV, and VIM, as shown in Figure 3.

Quintile 5 of ASV for triglyceride levels was associated with an increased risk for any coronary event compared to quintile 1 in model 4 (HR 1.35, 95% CI 1.14–1.60, $P = .0006$), as shown in Figure 4. Quintile 5 included patients with a triglyceride ASV of 53.7 and higher. Similar results were seen for the other measures of variability (not shown). For triglyceride variability, the increase in risk appeared to reside mainly in quintile 5, with risk in quintiles 1–4 being lower and approximately equal.

Quintiles of ASV for triglycerides are also shown in Figure 4 for the other study end points. For any CV event,

Figure 2   Risk of various events during follow-up in ASV quintiles of HDL-C variability. Results were similar for the other 3 measures of variability. Quintile 5 was associated with an increased risk for each end point except incident diabetes. *Adjusted for treatment + mean HDL-C + baseline factors (age, sex, race, BMI, diabetes mellitus, hypertension, smoking status, LDL-C, HDL-C, total cholesterol, triglycerides, chronic kidney disease, and heart failure). ASV, average successive variability; CV, cardiovascular; HDL-C, high-density lipoprotein cholesterol.
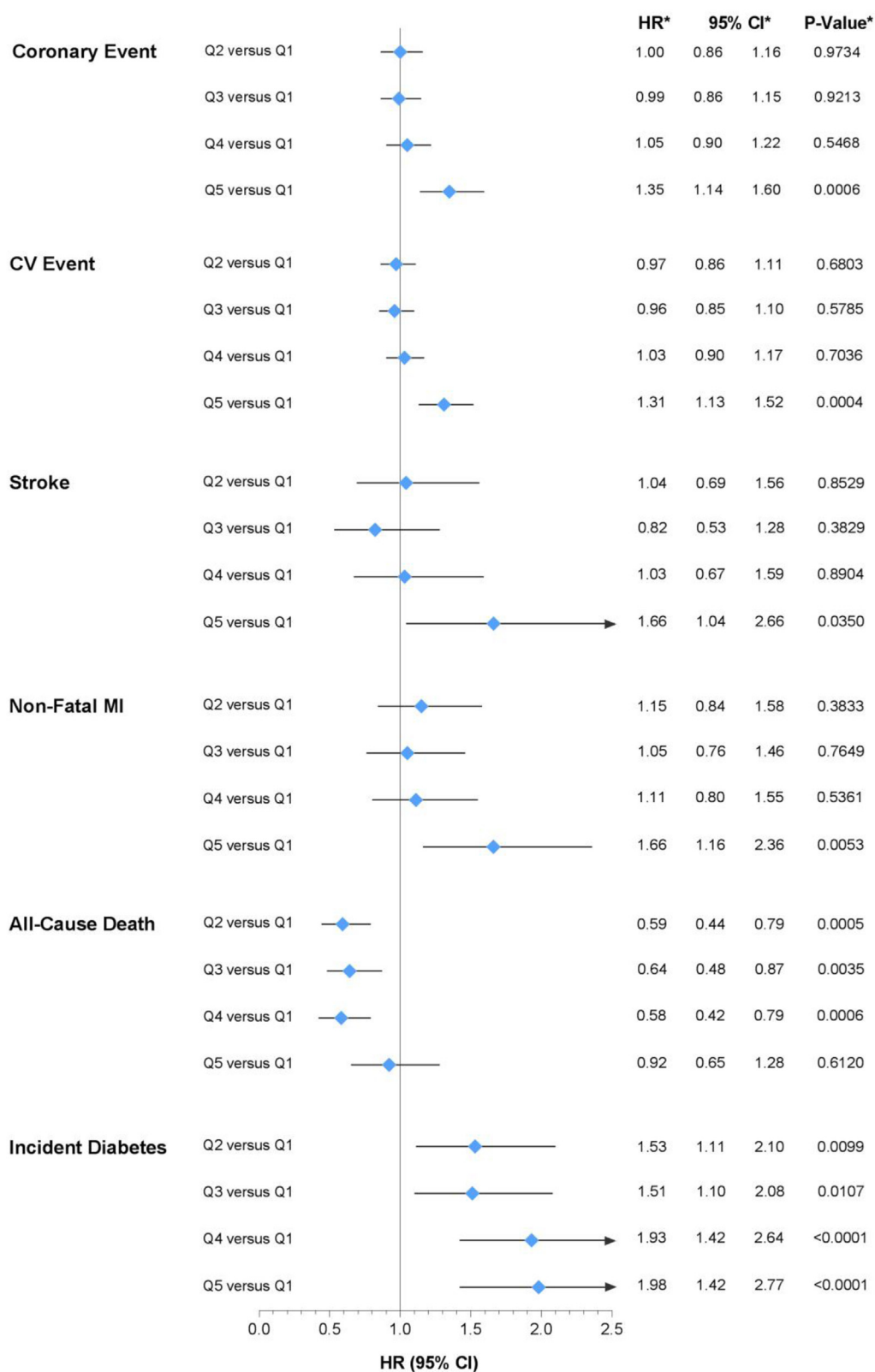
Figure 3   Risk of a coronary event in unadjusted and adjusted Cox regression models for 1 standard deviation of 4 measures of triglyceride variability: ASV, SD, CV, and VIM. *Baseline factors included age, sex, race, BMI, diabetes mellitus, hypertension, smoking status, LDL-C, HDL-C, total cholesterol, triglycerides, chronic kidney disease, and heart failure. ASV, average successive variability; CV, cardiovascular; SD, standard deviation; VIM, variability independent of the mean.

and for stroke, non-fatal MI, and incident diabetes, the HR was higher in quintile 5 compared to quintile 1, ranging from 1.31 to 1.98, and in each case, the trend across quintiles was statistically significant. For all-cause mortality, a trend in the opposite direction was observed, with a lower HR in quintile 5 compared to quintile 1 (HR 0.89, 95% CI 0.64–1.25, P = .51). This finding may be a result of the shorter follow-up and thus fewer lipid measurements among patients who died.

LDL-C variability and end point events

The relationship between LDL-C variability and events has already been reported[4] and is summarized here only for comparison. For each 1 SD increase in ASV of LDL-C, the risk of any coronary event increased in the unadjusted Cox model (HR 1.14, 95% CI 1.10–1.18, P < .0001) and in model 4, adjusted for treatment group, mean HDL-C, and clinical covariates (HR 1.14, 95% CI 1.09–1.19,

		HR*	95% CI*		P-Value*
Coronary Event	Q2 versus Q1	1.00	0.86	1.16	0.9734
	Q3 versus Q1	0.99	0.86	1.15	0.9213
	Q4 versus Q1	1.05	0.90	1.22	0.5468
	Q5 versus Q1	1.35	1.14	1.60	0.0006
CV Event	Q2 versus Q1	0.97	0.86	1.11	0.6803
	Q3 versus Q1	0.96	0.85	1.10	0.5785
	Q4 versus Q1	1.03	0.90	1.17	0.7036
	Q5 versus Q1	1.31	1.13	1.52	0.0004
Stroke	Q2 versus Q1	1.04	0.69	1.56	0.8529
	Q3 versus Q1	0.82	0.53	1.28	0.3829
	Q4 versus Q1	1.03	0.67	1.59	0.8904
	Q5 versus Q1	1.66	1.04	2.66	0.0350
Non-Fatal MI	Q2 versus Q1	1.15	0.84	1.58	0.3833
	Q3 versus Q1	1.05	0.76	1.46	0.7649
	Q4 versus Q1	1.11	0.80	1.55	0.5361
	Q5 versus Q1	1.66	1.16	2.36	0.0053
All-Cause Death	Q2 versus Q1	0.59	0.44	0.79	0.0005
	Q3 versus Q1	0.64	0.48	0.87	0.0035
	Q4 versus Q1	0.58	0.42	0.79	0.0006
	Q5 versus Q1	0.92	0.65	1.28	0.6120
Incident Diabetes	Q2 versus Q1	1.53	1.11	2.10	0.0099
	Q3 versus Q1	1.51	1.10	2.08	0.0107
	Q4 versus Q1	1.93	1.42	2.64	<0.0001
	Q5 versus Q1	1.98	1.42	2.77	<0.0001

HR (95% CI) axis: 0.0 0.5 1.0 1.5 2.0 2.5

Figure 4   Risk of various events during follow-up in ASV quintiles of triglyceride variability. Results were similar for the other 3 measures of variability. Quintile 5 was associated with an increased risk for each end point except all-cause mortality. *Adjusted for treatment + mean TG + baseline factors (age, sex, race, BMI, diabetes mellitus, hypertension, smoking status, LDL-C, HDL-C, total cholesterol, triglycerides, chronic kidney disease, and heart failure). ASV, average successive variability.

$P < .0001$). Similar results were seen for the other measures of variability: SD, CV, and VIM (data not shown).

Higher quintiles of ASV for LDL-C were associated with an increased risk for any coronary event. After adjusting for treatment group, mean LDL-C, and clinical covariates (model 4), the risk was 24% higher in quintile 5 compared to quintile 1 (HR 1.25, 95% CI 1.07–1.44, $P = .0037$). Similar results were seen for the other measures of variability (not shown). For the other study end points, the risk in quintile 5 compared to quintile 1 was 27% to 31% higher, although the increase was not statistically significant for stroke, nonfatal MI, or all-cause mortality. For incident diabetes, the HR for quintile 5 compared to quintile 1 for ASV of LDL-C was 1.30 (95% CI 0.99–1.71, $P = .060$).

Relationships between triglyceride, HDL-C, and LDL-C variability

The Pearson correlation coefficients among triglyceride, HDL-C, and LDL-C variability were all weak but highly statistically significant due to the large numbers. The correlation between triglycerides and HDL-C variability was 0.046, between triglycerides and LDL-C variability was 0.26, and between HDL-C and LDL-C variability was 0.16 ($P < .0001$ for all). Similar results were seen for SD.

In a model adjusted for treatment group, mean HDL-C, triglyceride, and LDL-C levels, and clinical covariates (model 4), and containing measures of HDL-C, triglyceride, and LDL-C variability, HDL-C and LDL-C variability remained robust predictors of time to first coronary event: the HR for 1 SD increase in ASV for HDL-C was 1.13 (95% CI 1.07–1.18, $P < .0001$) and for LDL-C was 1.10 (95% CI 1.05–1.16, $P < .0001$). Triglyceride variability was a weaker predictor: the HR for 1 SD increase in ASV for triglycerides was 1.05 (95% CI 1.00–1.11, $P = .0495$).

Discussion

The results of this study indicate that measures of visit-to-visit variability of triglycerides, HDL-C, and LDL-C are each predictive of coronary and CV events. The 4 measures of variability used in this study, ASV, SD, CV, and VIM, all yielded similar results. The ability of these measurements to predict events persisted after adjustment for treatment group (atorvastatin 10 mg or 80 mg/d), treatment group plus mean triglyceride, HDL-C or LDL-C level, and treatment group, mean lipid level, and a long list of clinical covariates: age, sex, race, BMI, diabetes, hypertension, current smoking, chronic kidney disease, heart failure, LDL-C, HDL-C, total cholesterol, and triglyceride levels.

After these adjustments, the incremental risk for any coronary event for quintile 5 vs quintile 1 of ASV was 35% for triglycerides, 50% for HDL-C, and 24% for LDL-C. The incremental risk for triglycerides was 66% for stroke

and 66% for nonfatal MI, and for HDL-C, it was 75% for stroke and 62% for nonfatal MI. This robust predictive power does not mean that variability in lipid measurements would be useful clinically for risk prediction because most risk predictors used in clinical practice are readily available, and the mechanism whereby the factor increases risk is understood. Such is not the case for lipid variability.

Mechanism of action

How variability in HDL-C, triglyceride, and LDL-C measurements relates to an increase in coronary events is unknown. All patients in this study were taking atorvastatin, and incomplete adherence to treatment would result in higher variability of LDL-C and triglyceride measurements. However, patients in a clinical trial tend to be more compliant with treatment compared to the usual clinical setting, and in our previous study of LDL-C variability,[4] the variability measures were predictive of events even after controlling for medication adherence. In any case, statins have comparatively little long-term effect on HDL-C, and thus, medication noncompliance is a poor explanation for HDL-C variability. Subjects who do discontinue statins have been shown to be at higher risk for subsequent MI and CV death.[10]

Interestingly, variability of one lipid measurement did not correlate well with the variability of the others. This suggests that the mechanisms causing higher variability of HDL-C measurements, for example, may differ from the mechanisms causing higher variability in LDL-C or triglyceride measurements.

Higher levels of HDL-C, triglycerides, and LDL-C were associated with higher variability of each parameter. Otherwise, the clinical features of patients with HDL-C or LDL-C variability above and below the median (Tables 1–3) were generally unremarkable. However, patients with triglyceride variability above the median were younger, more likely had diabetes and a higher BMI, and had higher LDL-C and lower HDL-C levels, as well as much higher triglyceride levels, compared to those below the median. The metabolic syndrome is thus likely associated with high triglyceride variability.

Another potential mechanism of this increased risk is that lipid variability is an epiphenomenon of other conditions that increase CV risk. Perhaps patients with systemic conditions causing general frailty might have higher variability of multiple biological parameters and increased risk caused by several pathologic mechanisms. If higher variability were related to frailty, patients with increased variability might be expected to be older, but they were not in this study.

Triglyceride levels vary widely during the day, mainly in relation to meals, and nonfasting triglyceride levels predict CV events at least as well as fasting levels do.[11,12] Postprandial hypertriglyceridemia induces transient endothelial dysfunction, a marker of early atherosclerosis.[13,14] This short-term variability in fasting triglycerides is different than the visit-to-visit variability described in this study. Given the high short-term variability in triglycerides, it is

surprising that visit-to-visit variability is also of prognostic importance.

Incident diabetes

High triglyceride levels, but not high LDL-C or low HDL-C levels, have been shown to be an independent risk factor for incident diabetes in the TNT population.[15] In this study, triglyceride variability, but not HDL-C variability, was predictive of incident diabetes in the model adjusted for treatment group, mean lipid level, and clinical features. Many clinical and laboratory markers that predict incident diabetes have been identified, and high triglyceride variability might be associated with one or more of them. As noted previously, high triglyceride variability was associated with features of the metabolic syndrome in this study, and the metabolic syndrome is a strong predictor of incident diabetes.

Previous studies

The amount of variability in clinical lipid measurements has been well documented.[16–18] A fixed component of this variability is due to laboratory measurement variability, but most is due to intrapatient variability.[16] In contrast to BP variability, where many studies have reported an association between high variability and CV events, few reports have linked variability in lipid measurements to CV events.[19,20] In a study of 130 survivors of ST segment-elevation MI, LDL-C, and HDL-C predicted CV events over a 5-year follow-up.[19]

In a study of 4428 participants of Prospective Study of Pravastatin in the Elderly at Risk, higher LDL-C variability was recently found to be associated with lower cognitive function and lower cerebral blood flow in both the placebo and pravastatin treatment arms.[20] HDL-C and triglyceride variability were not reported in this study, and the authors speculated on potential mechanisms that could explain their findings.

Limitations of the study

The results of this study were derived from a clinical trial where conditions differ from clinical practice. Lipids were measured after a 12-hour fast and analyzed in a central laboratory. The study patients all had documented coronary disease and were taking atorvastatin. We used 4 measures of variability and all 4 yielded roughly similar results. However, it is not known whether or not our findings could be duplicated under other conditions, such as clinical practice. The variability measurements do not take into account the direction of the change; however, adjusting for change in lipid values from week 12 to the end of the study did not alter our findings.

As a retrospective analysis of a clinical trial, our study does not provide an explanation for its findings. How variability in HDL-C, triglyceride, and LDL-C measurements relate to coronary events or incident diabetes appears to be a fruitful topic for further investigation.

Conclusions

Visit-to-visit variability in fasting measurements of HDL-cholesterol, triglycerides, and LDL-cholesterol are predictive of coronary events, CV events, and for triglyceride and LDL-C variability, incident diabetes. The mechanisms accounting for these associations remain to be determined.

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