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Original Article

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.

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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