Materials and Methods

From pooled data of 7 prospective atherosclerosis progression/regression IVUS trials, including 3479 stable patients with established coronary artery disease (CAD), we identified 647 statin naive patients who were commenced on statin therapy. We defined hyporesponder to statin therapy as a percentage reduction of LDL-C < 15%. Seven studies included in the current analysis were the REVERSAL (Reversal of Atherosclerosis With Aggressive Lipid Lowering) study, the CAMELOT (Comparison of Amlodipine Versus Enalapril to Limit Occurrences of Thrombosis) study, the ACTIVATE (Acyl:Cholesterol Acyltransferase Intavascular Atherosclerosis Treatment Evaluation) study, the ASTEROID (A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden) trial, the ILLUSTRATE (Investigation of Lipid Level Management Using Coronary Ultrasound to Assess Reduction of Atherosclerosis by Cholesteryl Ester Transfer Protein Inhibition and High-Density Lipoprotein Elevation) study, the PERISCOPE (Comparison of Pioglitazone Versus Glimepiride on Progression of Coronary Atherosclerosis in Patients With Type 2 Diabetes) trial, and the STRADIVARIUS (Effect of Rimonabant on Progression of Atherosclerosis in Patients With Abdominal Obesity and Coronary Artery Disease) study. All patients were required to have coronary artery disease, defined as having at least 1 lumen narrowing >20% in a major epicardial coronary artery on a diagnostic coronary angiogram performed for a clinical indication. Each study was approved by the institutional review boards of the participating clinical trial sites, and all participants in the trials provided informed written consent before enrollment.

Acquisition and analysis of IVUS images

The methods for acquisition and analysis of IVUS images have been described previously. In brief, a target vessel without luminal stenosis > 50% within a segment of at least 30 mm in length was selected for imaging. This vessel was
required not to have undergone previous revascularization or represent the culprit vessel for a prior myocardial infarction. After anticoagulation therapy and administration of intracoronary nitroglycerin, an imaging catheter containing a high-frequency ultrasound transducer (30 to 40 MHz) was inserted distally within coronary artery. Ultrasonic images were continuously recorded on videotape during withdrawal of the catheter at a constant rate of 0.5 mm/s. Imaging was performed within the same coronary artery at baseline and at the end of the study, which ranged from 18 to 24 months.

The recorded images were digitized for subsequent analysis. An anatomically matched segment was defined at the 2 time points on the basis of proximal and distal side branches (fiduciary points). Cross-sectional images spaced precisely 1 mm apart were selected for measurement. The leading edges of the lumen and external elastic membrane (EEM) were traced by manual planimetry. Plaque area was defined as the area occupied between these leading edges. The percent atheroma volume (PAV) was calculated as the proportion of the entire vessel wall occupied by atherosclerotic plaque:

$$\text{PAV} (%) = \frac{\sum (EEM_{\text{area}} - \text{LUMEN}_{\text{area}})}{\sum EEM_{\text{area}}} \times 100$$

Volumes occupied by the lumen and EEM were similarly calculated by summation of their respective areas in each measured image and subsequently normalized to account for differences in segment length between subjects.

Substantial plaque progression and regression was pre-specified as a > 5% relative increase or decrease in PAV. A remodeling index was defined as change in EEM volume during the course of the study.

**Statistical Analysis**

Patients were stratified according to the presence or absence of hyporesponse to statin therapy. Results are presented as percentages for categorical variables and mean ± standard deviation for continuous variables. When variables were not
normally distributed, their results are expressed as median (interquartile range). Clinical and plaque characteristics were compared by the Student’s t-test or Wilcoxon rank-sum test for continuous variables as appropriate. For categorical variables, the Pearson chi-square test or Fisher’s exact test were used. Changes in measures of atheroma burden were compared by analysis of covariance, after controlling for baseline values, baseline clinical characteristics including type of statin use and its dose, and trial, and expressed as least squares mean ± standard error. Tests were two-tailed with a 0.05 significance level. All statistical analyses were performed using the SAS software, version 9.2 (SAS Institute Inc, Cary, North Carolina).

References


