MATERIALS AND METHODS

Study population
The present analysis included all patients who participated in 9 clinical trials assessing the impact of medical therapies on serial changes in coronary atheroma burden using IVUS. Included in this analysis were trials assessing intensive lipid lowering with statins [REVERSAL (Reversal of Atherosclerosis With Aggressive Lipid Lowering), ASTEROID (A Study to Evaluate the Effect of Rouvastatin on Intravascular-Ultrasound Derived Indices of Coronary Atheroma Burden) and SATURN (The Study of Coronary Atheroma by Intravascular Ultrasound: Effect of Rosuvastatin Versus Atorvastatin)], anti-hypertensive therapies [AQUARIUS (Aliskiren Quantitative Atherosclerosis Regression Intravascular Ultrasound Study) and NORMALIZE (Norvasc for Regression of Manifest Atherosclerotic Lesions by Intravascular Sonographic Evaluation)], the anti-atherosclerotic efficacy of acyl-coenzyme A:cholesteryl ester transfer protein inhibition [ACTIVATE (ACAT Intravascular Atherosclerosis Treatment Evaluation)], cholesteryl ester transfer protein inhibition [ILLUSTRATE (Investigation of Lipid Level Management Using Coronary Ultrasound to Assess Reduction of Atherosclerosis by CETP Inhibition and HDL Elevation)], endocannabinoid receptor antagonism [STRADIVARIUS (Strategy to Reduce Atherosclerosis Development Involving Administration of Rimonabant – The Intravascular Ultrasound Study)], and the peroxisome proliferator-activated receptor-gamma agonism [PERISCOPE (Pioglitazone Effect on Regression of Intravascular Sonographic Coronary Obstruction Prospective Evaluation)].

Acquisition and analysis of serial IVUS images
The acquisition and serial analysis of IVUS images in each of these trials has been previously described in detail. Briefly, target vessels for imaging were selected if they contained no luminal stenosis >50% angiographic severity within a segment of at least 30 mm length. Imaging was performed within the same coronary artery at baseline and at study completion, which ranged from 18 to 24 months. Imaging in all trials was screened by the Atherosclerosis Imaging Core Laboratory of the Cleveland Clinic Coordinating Center for Clinical Research. Patients meeting pre-specified requirements for image quality were eligible for randomization. An anatomically matched segment was defined at the two 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. 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 accuracy and reproducibility of this method have been reported previously. The percent atheroma volume (PAV) was determined by calculating the proportion of the entire vessel wall occupied by atherosclerotic plaque, throughout the segment of interest as follows:

$$ PAV = \frac{EEM_{area} - Lumen_{area}}{EEM_{area}} \times 100 $$
Statistical analysis

Continuous variables were reported as mean ± SD if normally distributed and as median (interquartile range) if non-normally distributed. Non-HDL-C levels were calculated as [total cholesterol – HDL-C] mg/dL. Demographics, baseline clinical characteristics, medication use, laboratory biochemical data, and baseline IVUS parameters were compared.

The LOWESS method was used to visually assess the overall relationship between achieved non-HDL-C and TG levels against changes in PAV. Correlations between variables (change in PAV and on-treatment non-HDL-C, TG and LDL-C) are described with the use of Spearman rank-correlation coefficients. The effects of on-treatment non-HDL-C and TG levels upon coronary atheroma progression were analyzed by stratifying patients according to lower (<100 mg/dL) versus higher (≥100 mg/dL) non-HDL-C levels, lower (<200 mg/dL) versus higher (≥200 mg/dL) and TG levels across differing patient populations (i) on-treatment LDL-C <70 versus ≥70 mg/dL, (ii) on-treatment CRP <2 versus ≥2 mg/L, (iii) non-diabetic versus diabetic patients. Given that the calculation of non-HDL-C inherently include LDL-C, comparative multivariable linear mixed-effects regression models were constructed to evaluate predictors of PAV progression according to on-treatment non-HDL-C and LDL-C, respectively. Furthermore, restricted cubic splines were plotted to visualize these relationships (Supplementary file). Robustness of the models was demonstrated through model validation using residual diagnostics, and collinearity was evaluated to be at an acceptable level.

We performed sensitivity analyses to evaluate the time-to-first major adverse cardiovascular event (MACE, defined as cardiovascular death, non-fatal myocardial infarction, stroke, coronary revascularization, hospitalization for unstable angina). Separate log-rank tests with Kaplan-Meier curves were performed on MACE rates according to the strata of on-treatment non-HDL-C levels (< vs. ≥median), achieved LDL-C levels (< vs. ≥median), achieved TG levels (< vs. ≥median) and achieved TG levels (< vs. ≥200 mg/dL). A 24-month cut-off period was used for the survival analysis, and the time to first occurrence of MACE was determined. Patients without a MACE at 24-months were censored at this time point. Both the IVUS and MACE analyses were based on the patient population that had baseline and achieved IVUS measurements and had non-missing on-treatment lipoprotein or TG records. A 2-sided P-value <0.05 was considered statistically significant. All analyses were performed using SAS software version 9.2 (SAS Institute, Cary, North Carolina), and the bootstrapping on mixed model beta-coefficients was conducted using the R software.
REFERENCES


