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Lipoprotein(a) and coronary atheroma progression rates during long-term high-intensity statin therapy: Insights from SATURN

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ABSTRACT

Background & aims: Lipoprotein(a) [Lp(a)] is a low-density lipoprotein (LDL)-like particle that associates with major adverse cardiovascular events (MACE). We examined relationships between Lp(a) measurements and changes in coronary atheroma volume following long-term maximally-intensive statin therapy in coronary artery disease patients.

Methods: Study of coronary atheroma by intravascular ultrasound: Effect of Rosuvastatin Versus Atorvastatin (SATURN) used serial intravascular ultrasound measures of coronary atheroma volume in patients treated with rosuvastatin 40 mg or atorvastatin 80 mg for 24 months. Baseline and follow-up Lp(a) levels were measured in 915 of the 1039 SATURN participants, and were correlated with changes in percent atheroma volume (ΔPAV).

Results: Mean age was 57.7 ± 8.6 years, 74% were men, 96% were Caucasian, with statin use prior to study enrolment occurring in 59.3% of participants. Baseline [median (IQR)] LDL-cholesterol (LDL-C) and measured Lp(a) levels (mg/dL) were 114 (99, 137) and 17.4 (7.6, 52.9) respectively; follow-up measures were 60 (47, 77), and 16.5 (6.7, 57.7) (change from baseline: $p < 0.001$, $p = 0.31$ respectively). At baseline, there were 676 patients with Lp(a) levels <50 mg/dL [median Lp(a) of 10.9 mg/dL], and 239 patients with Lp(a) levels ≥ 50 mg/dL [median Lp(a) of 83.2 mg/dL]. Quartiles of baseline and follow-up Lp(a) did not associate with ΔPAV. Irrespective of the achieved LDL-C (<*vs.* ≥70 mg/dL), neither baseline nor on-treatment (<*vs.* ≥median) Lp(a) levels significantly associated with ΔPAV. No significant differences were observed in ΔPAV in Lp(a) risers *versus* non-risers, nor in those patients with baseline or on-treatment Lp(a) levels < *vs.* > 50 mg/dL.

Conclusions: In coronary artery disease patients prescribed long-term maximally intensive statin therapy with low on-treatment LDL-C levels, measured Lp(a) levels (predominantly below the 50 mg/dL threshold) do not associate with coronary atheroma progression. Alternative biomarkers may thus associate with residual cardiovascular risk in such patients.

Abbreviations: SATURN, Study of Coronary Atheroma by Intravascular Ultrasound: Effect of Rosuvastatin Versus Atorvastatin; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride; CRP, C-reactive protein; Lp(a), lipoprotein(a); PAV, percent atheroma volume; MACE, major adverse cardiovascular events.

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1. Introduction

Several lines of evidence point to lipoprotein(a) [Lp(a)], a genetically determined atherogenic lipoprotein composed of apolipoprotein (apo) B-100 bound to apo(a) harboring oxidized phospholipids, as a causal mediator for cardiovascular disease. Epidemiological meta-analyses sampling a range of studies spanning across 4 decades revealed continuous, independent relationships between Lp(a) concentrations and cardiovascular risk [1]. Mendelian randomization and genome-wide association studies establish that genetically determined Lp(a) elevations associate with myocardial infarction rates and cardiovascular events [2–4].

To date, statin-mediated low-density lipoprotein cholesterol (LDL-C) lowering is the dominant approach to lowering clinical events in individuals across broad atherosclerotic risk categories [5,6]. Numerous studies demonstrate the proatherosclerotic effects of elevated Lp(a) levels in the presence of concomitantly elevated LDL-C [7–13], but not necessarily when LDL-C concentrations are lower, or already well controlled with statins. The contribution of Lp(a) levels to residual atherosclerotic risk in the setting of concomitant/background statin-mediated significant LDL-C lowering amongst individuals with established atherosclerotic disease remains poorly understood.

Study of Coronary Atheroma by Intravascular Ultrasound: Effect of Rosuvastatin Versus Atorvastatin (SATURN; ClinicalTrials.gov number: NCT00620542) was the largest imaging trial comparing the antiatherosclerotic efficacy of 2 of the most potent statin regimens (rosuvastatin 40 mg *vs.* atorvastatin 80 mg), by measuring the change in coronary atheroma volume on serial intravascular ultrasonography (IVUS) [14]. No appreciable difference of the primary efficacy endpoint of change in percent atheroma volume (ΔPAV), safety, or clinical event rates was found between the 2 treatment groups [15]. This pre-specified *post hoc* analysis of SATURN tested the hypothesis that measures of Lp(a) associate with coronary atheroma progression-regression in patients with coronary artery disease treated with 24 months of maximally intensive statin therapy. As a sensitivity analysis, we also examined for associations between Lp(a) levels and major adverse cardiovascular events (MACE).

2. Patients and methods

2.1. Patient selection

The design of SATURN has been previously described [14]. In brief, patients with angiographically demonstrated coronary disease and LDL-C <116 mg/dL following a 2-week treatment period with atorvastatin 40 mg or rosuvastatin 20 mg daily were re-randomly assigned and treated for 24 months with atorvastatin 80 mg or rosuvastatin 40 mg daily. Subjects underwent IVUS imaging of a coronary artery at baseline and following 104 weeks of treatment.

2.2. Acquisition and analysis of intracoronary ultrasonic imaging

The presence of at least a single lumen stenosis of >20% angiographic stenosis in an epicardial coronary artery at the time of a clinically indicated coronary angiogram was necessary for enrolment eligibility. IVUS was performed at baseline in a single, native coronary artery with no lumen stenosis of >50% severity, which had not undergone revascularization and was not considered to be the culprit vessel of a prior myocardial infarction (MI). Images were screened by the Atherosclerosis Imaging Core Laboratory of the Cleveland Clinic Center for Clinical Research for quality, and those patients whose baseline imaging met these requirements, were eligible for randomization. Following 104 weeks of treatment, patients underwent a second IVUS of the same artery. Anatomically matched arterial segments were selected for analysis on the basis of proximal and distal landmarks. Cross-sectional images spaced 1 mm apart were selected for analysis, with lumen and external elastic membrane (EEM) leading edges defined by manual planimetry. Plaque area was determined as the area between these leading edges. Percent atheroma volume (PAV), a measure of plaque burden, was calculated as previously described [16]. Change in plaque burden was calculated as the PAV at 104 weeks minus the corresponding PAV at baseline (ΔPAV). Plaque regression was defined as any decrease in PAV from baseline.

2.3. Lp(a) laboratory measurements

Lp(a) concentrations were measured in a blinded manner at the Atherosclerosis Clinical Research Laboratory (ACRL) at Baylor College of Medicine using a commercially available latex-enhanced turbidimetric immunoassay (Denka Seiken, Ltd., Tokyo, Japan). This assay is insensitive to the kringle IV type 2 repeats within apo(a) and uses apo(a) calibrators with mixed molecular weights to minimize apo(a) size-dependent biases associated with Lp(a) measurements [17]. Mean inter-assay coefficients of variation for the assay were 4.75%, 2.25% and 3.07% at Lp(a) concentrations of 10.7, 53.2 and 139.2 mg/dL, respectively.

2.4. Statistical analysis

Of the 1039 SATURN participants, 915 patients had non-missing baseline and follow-up Lp(a) values. Continuous variables were reported as mean ± SD if normally distributed and as median (interquartile range) if non-normally distributed. Plaque progression was defined as changes in PAV greater than zero.

Demographics, medical history and baseline medications were presented for the overall SATURN and SATURN Lp(a) populations respectively. Baseline and follow-up laboratory biochemical measures as well as changes from baseline were compared between concomitant atorvastatin and rosuvastatin therapy. Plaque progression-regression status, represented by (i) absolute change in PAV (or ΔPAV) and (ii) PAV progression rate, were compared across quartiles of Lp(a) measures (baseline and follow-up) by a trend test. To evaluate further the impact of Lp(a) on ΔPAV and MACE (defined as death, non-fatal myocardial infarction, stroke, coronary revascularization or hospitalization for unstable angina) in the context of lipid and inflammatory factors, the same baseline and follow-up Lp(a) measures, dichotomized by their respective median values, were assessed for their relationship with PAV progression (via binary logistic regression) and MACE (via Cox proportional hazards regression), stratified by on-treatment LDL-C <70 *versus* ≥70 mg/dL, and by on-treatment CRP <2 *versus* ≥2 mg/L. Furthermore, changes in Lp(a)-C levels were categorized as risers against non-risers, defined by the change value > 0 *versus* ≤0. Baseline clinical characteristics, biochemical and IVUS variables in patients with rising Lp(a) levels were compared with those with non-rising Lp(a) levels. A 2-sided probability value of 0.05 was considered statistically significant. All the analyses were performed using the SAS software version 9.4 (SAS Institute, Cary, North Carolina).

3. Results

3.1. Patient characteristics

Table 1 summarizes baseline clinical characteristics of the study population. Mean age was 57.8 ± 8.6 years, 74% were men, 96%