Elevated Lipoprotein(a) is Associated with Statin Resistance

Gary S. Ma, MD, Sotirios Tsimikas, MD, Calvin Yeang, MD, PhD

Division of Cardiovascular Diseases, Sulpizio Cardiovascular Center, University of California, San Diego, La Jolla, California, USA

Background:
LDL-C reduction by statins is the cornerstone in pharmacologic therapy for atherosclerotic cardiovascular disease (ASCVD) risk reduction. Despite adherence to statins, some patients fail to achieve LDL-C goals (i.e., 50% reduction on a high intensity statin), a phenomenon known as statin resistance. Due to a lack of clinically useful predictors, statin resistance is recognized only after a 6-8 week empiric trial of therapy. All clinical LDL-C assays include the cholesterol content on both lipoprotein(a) [Lp(a)] and LDL particles. Because statins do not lower and can increase Lp(a), the cholesterol on Lp(a) may represent a statin insensitive pool within LDL-C.

Objective:
The role of elevated baseline Lp(a) as a cause of statin resistance was investigated in patients treated with high-intensity statin therapy.

Methods:
A secondary analysis was performed on 2338 participants from the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) trial, randomized to receive either atorvastatin 80mg or placebo, in which baseline and week 16 lipid parameters were analyzed.

Results:
In the atorvastatin group (n = 1092), the mean (S.D.) baseline LDL-C, absolute LDL-C reduction, median percent LDL-C change from baseline (IQR), and Lp(a) were 123.8 (33.5) mg/dL, 52.2 (36.7) mg/dL, -47.6% (-59.1—-29.9%), and 10.6 (5.1 – 29.1) mg/dL, respectively. Median (IQR) baseline Lp(a) was higher [12.1 (5.9—38.1) mg/dL vs 9.2 (4.4—22.4) mg/dL, Mann-Whitney p < 0.001] in patients with attenuated percent LDL-C reduction compared to group median. Compared to the lowest baseline Lp(a) tertile, the percent LDL-C reduction on atorvastatin was significantly attenuated in the tertiles with higher Lp(a) [Figure 1A]. The median percent LDL-C reduction on atorvastatin was 42.3% (24.3—52.5%) in patients with baseline Lp(a) between 50 – 99 mg/dL prevalent in ~30% of the population, and 32.6% (11.5—43.7%) with Lp(a) > 100 mg/dL prevalent in ~10% of the population, both significantly attenuated compared with that in patients with baseline Lp(a) < 30 mg/dL (50.0% (33.3—61.1%), p < 0.001 [Figure 1B]. An LDL-C target of 70 mg/dL or less was achieved in 62.3% of patients with baseline Lp(a) 0 – 29 mg/dL, compared to 55.2%, 43.3%, and 24.1% of those with Lp(a) 30 – 49 mg/dL, 50 – 99 mg/dL, and ≥ 100 mg/dL (Chi-square p < 0.001), respectively [Figure 2].

Conclusions:
Elevated Lp(a), common in the population, is associated with statin resistance and may identify patients who require additional or more potent lipid lowering therapies to achieve LDL-C goals.
Figure 1: Association between Lp(a) tertiles (A), clinically relevant Lp(a) thresholds (B) and percent LDL-C change with atorvastatin.

A. 

![Graph A showing percent change in LDL-C for different Lp(a) tertiles.

B. 

![Graph B showing percent change in LDL-C for different Lp(a) levels.

Figure 2: Relationship between baseline Lp(a) levels and proportion of patients with achieved LDL-C < 70 mg/dL following treatment with atorvastatin.

![Graph showing number of patients achieving LDL-C < 70 mg/dL at different Lp(a) levels.

- 62.3% (513/824) for 0-29 mg/dL
- 55.2% (58/105) for 30-49 mg/dL
- 43.3% (58/134) for 50-99 mg/dL
- 24.1% (7/29) for ≥100 mg/dL

- Achieved LDL-C <70mg/dL
- LDL >70 mg/dL