Letter Regarding Article by Tsimikas et al, "High-Dose Atorvastatin Reduces Total Plasma Levels of Oxidized Phospholipids and Immune Complexes Present on Apolipoprotein B-100 in Patients With Acute Coronary Syndromes in the MIRACL Trial"
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Letter Regarding Article by Tsimikas et al, “High-Dose Atorvastatin Reduces Total Plasma Levels of Oxidized Phospholipids and Immune Complexes Present on Apolipoprotein B-100 in Patients With Acute Coronary Syndromes in the MIRACL Trial”

To the Editor:

Tsimikas et al hypothesized that in the MIRACL (Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering) study statins induced a net efflux of oxidized phospholipids (OxPL) from the vessel wall, which is reflected by an increased OxPL/apoB ratio, representing enrichment in OxPL of apoB particles. We would like to suggest an alternative interpretation. The oxidized low-density lipoprotein (OxLDL)-E06 assay used captures apoB-containing particles from the plasma sample. Because plasma lipoprotein(a) (Lp(a)) increased and LDL decreased during statin treatment, more Lp(a) and fewer LDL particles were captured after statin treatment. Because OxPL are predominantly associated with Lp(a), the increased OxPL/apoB ratio could be explained by the shift in the Lp(a)/LDL ratio. Similarly, in the placebo-treated group the decreased OxPL/apoB ratio results from a decrease in Lp(a) relative to LDL. It is therefore unlikely that the OxPL/apoB ratio is a surrogate marker of net removal of OxPL from the vessel wall. Moreover, the observed 30% decrease in total plasma apoB-OxPL also argues against an increased net efflux of OxPL from the vessel wall. Recently, using the OxLDL assay from Mercodia in which an oxidation epitope associated with apoB is detected with monoclonal antibody 4E6, we found that atorvastatin (80 mg/d) and simvastatin (40 mg/d) reduced total plasma Ox-apoB (43% and 35%, respectively) in patients with familial hypercholesterolemia from the ASAP study. Interestingly, we observed no change in the Ox-apoB/apoB ratio when we used the noncompetitive version of the kit, in which the immobilized antibody captures Ox-apoB from the sample. We did, however, observe a small increase in the Ox-apoB/apoB ratio (18% for atorvastatin, 13% for simvastatin) when we used the competitive version, which unlike the noncompetitive version is sensitive to the number of oxidation epitopes associated with apoB. In addition, the increase in Ox-apoB/apoB ratio can be explained by an increase in Lp(a) relative to LDL. To further address this question, measurements of OxLDL with E06 and 4E6 in well-designed assays (eg, in isolated Lp(a) particles) at different time points after the start of statin treatment are required.

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Response

We thank Van Tits et al for their interesting analysis of our data. Although we cannot absolutely rule out that their interpretation is correct, we strongly favor our interpretation for the following reasons: (1) 4E6 binds malondialdehyde-lysine epitopes on LDL, which have not been documented to be present on Lp(a) per se, and does not bind the OxPL that are recognized by E06 and present on Lp(a). Thus, the increase in their “oxidized apoB/apoB” ratio cannot be explained by increased Lp(a) levels. (2) Similar increases in OxPL/apoB and Lp(a) were noted in response to low-fat diets and immediately after angioplasty, in which only 50% of the OxPL were physically present on Lp(a), whereas the rest were on non-Lp(a) apoB-containing lipoproteins, conditions under which one may postulate efflux of OxPL from the vessel wall. (3) As pointed out in the Discussion in our original article, our hypothesis is strongly supported by unpublished studies in animals, including rabbits that do not have Lp(a), showing similar increases in OxPL/apoB with concomitant decreases in total OxPL-apoB and reduced vessel wall immunostaining for OxPL in response to regression diets. Therefore, the increased OxPL/apoB that accompanies lesion regression is clearly not the result of changes in Lp(a). We have additional evidence in humans that Lp(a) is the preferential (but not obligatory) acceptor of OxPL, which explains the strong association with Lp(a).

Unlike the OxPL/apoB measure, the Mercodia OxLDL assay strongly correlated with LDL (r = -0.70) in multiple studies and may not be independent of LDL. The methodology for the competition assay is not described and therefore we are unable to assess whether the parameters the authors describe are independent of apoB.

Comparative studies of current OxLDL assays are needed to understand their clinical utility. We agree that a focus of ongoing research should be to test the hypothesis that Lp(a) binding of OxPL is an innate immune mechanism to clear proinflammatory OxPL, and in particular to understand the mechanisms responsible for the increase in Lp(a) levels in response to statins or low-fat diets.

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