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"
Lambertus J. van Tits, Jacqueline de Graaf and Anton F. Stalenhoef

_Circulation_. 2005;111:e284-e285
doi: 10.1161/01.CIR.0000164264.00913.6D
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2005 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/111/18/e284

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org/subscriptions/
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.

Lambertus J. van Tits, PhD
Jacqueline de Graaf, MD, PhD
Anton F. Stalenhoef, MD, PhD
Department of General Internal Medicine
Radboud University Nijmegen Medical Centre
Nijmegen, The Netherlands
B.vantits@aig.umcn.nl

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.

Sotirios Tsimikas, MD
Joseph L. Witztum, MD
Elizabeth R. Miller, BS
Department of Medicine
University of California
San Diego, Calif
stsimikas@ucsd.edu

William J. Sasiela, PhD
Michael Szarek, SM
Pfizer Pharmaceuticals Group
New York, NY

Anders G. Olsson, MD, PhD
Department of Medicine and Care
Faculty of Health Sciences
University of Linköping
Linköping, Sweden

Gregory G. Schwartz, MD, PhD
Cardiology Division
Veterans Affairs Medical Center
University of Colorado Health Sciences Center
Denver, Colo


