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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Background—Oxidized phospholipids (OxPL) are present within atherosclerotic plaques and bound by lipoprotein (a) [Lp(a)] in plasma. This study evaluated the impact of atorvastatin on oxidized LDL (OxLDL) in patients with acute coronary syndromes (ACS).

Methods and Results—OxLDL-E06 (OxPL content on apolipoprotein B-100 [apoB] detected by antibody E06), apoB-100 immune complexes (apoB-IC), OxLDL autoantibodies, and Lp(a) levels were measured in 2341 patients at baseline and after 16 weeks of treatment with atorvastatin 80 mg/d or placebo. The OxLDL-E06 and apoB-IC data are reported per apoB-100 particle (OxPL/apoB, IC/apoB) and as total levels on all apoB-100 particles (total apoB-OxPL and total apoB-IC [eg, OxPL/apoB or IC/apoB×apoB-100 levels]). Compared with baseline values, atorvastatin reduced apoB-100 (−33%), total apoB-OxPL (−29.7%), total apoB-IC IgG (−29.5%), and IgM (−25.7%) (P<0.0001 for all), whereas no change or an increase was observed with placebo. When normalized per apoB-100, compared with placebo, atorvastatin increased OxPL/apoB (9.5% versus −3.9%, P<0.0001) and Lp(a) (8.8% versus −0.7%, P<0.0001). A strong correlation was noted between OxPL/apoB and Lp(a) (R=0.85, P<0.0001), consistent with previous data that Lp(a) binds OxPL.

Conclusions—After atorvastatin treatment, total OxPL on all apoB-100 particles was decreased. However, there was enrichment of OxPL on a smaller pool of apoB-100 particles, in parallel with similar increases in Lp(a), suggesting binding by Lp(a). These data support the hypothesis that atorvastatin promotes mobilization and clearance of proinflammatory OxPL, which may contribute to a reduction in ischemic events after ACS. (Circulation. 2004;110:1406-1412.)

Key Words: atherosclerosis ■ antibodies ■ lipoproteins ■ oxidation

Randomized trials have clearly shown that hydroxymethylglutaryl (HMG)-CoA reductase inhibitors (statins) reduce all-cause mortality and cardiovascular events in patients with stable coronary artery disease (CAD) when given over a period of 5 years.1,2 Retrospective3 and observational4 studies have also suggested that statins given to patients with acute coronary syndromes (ACS) improve event-free survival over a period of 1 year. The MIRACL study demonstrated that in-hospital initiation of 80 mg atorvastatin reduced recurrent ischemic events over a 16-week period.5 The PRavastatin Or atorVastatin Evaluation and Infection Therapy (PROVE-IT) study recently demonstrated superior outcomes in patients with ACS after 2 years of treatment with 80 mg atorvastatin versus 40 mg pravastatin, resulting in median LDL cholesterol levels of 62 and 95 mg/dL, respectively.6

The mechanisms underlying the early benefits of statins are not well delineated but have been attributed to plaque stabilization.7,8 However, it is not established whether statins exert their benefits primarily through reduction of LDL cholesterol alone and/or through additional pleiotropic effects, such as direct antiinflammatory or antioxidant actions.9 Although statins have been shown to reduce in vitro measures of oxidative stress (reviewed in Norata et al10), their effects on plasma OxLDL levels in patients, particularly those with ACS, are not well known.

Increased levels of OxLDL in the vessel wall and circulation are present in patients with unstable or “vulnerable”...
plaque,11,12 and associated with endothelial dysfunction.15,17 In mouse and rabbit aortic atherosclerotic lesions, OxLDL becomes depleted after regression diets, out of proportion to LDL depletion or other measures of plaque regression.8,18 These reductions in OxLDL are associated with increased collagen and smooth muscle cell content, increased endothelial nitric oxide synthase production, and reduced inflammatory markers,7 which suggests that removal of OxLDL from the vessel wall may serve as an early marker of plaque stabilization. In this analysis of the MIRACL trial, we determined whether favorable changes in plasma OxLDL levels might provide insights into the early clinical benefits of intensive statin treatment after ACS.

Methods

Study Design and Patient Sample

The MIRACL study design was published previously.5 Briefly, the study recruited 3086 patients with unstable angina or non–Q-wave acute myocardial infarction between 24 and 96 hours after hospital admission at 122 centers in 19 countries. Patients were randomly assigned to double-blind treatment with atorvastatin 80 mg/d or placebo for 16 weeks. The primary efficacy measure was the time to first occurrence of death, nonfatal acute myocardial infarction, cardiac arrest with resuscitation, or worsening angina with new objective evidence of ischemia and requiring emergency rehospitalization. In all, 2739 patients completed the entire 16-week follow-up period, of whom 2442 had baseline blood samples and 2341 had baseline and week 16 blood samples available for analysis. Blood samples were included to detect potential variations between microtiter plates. Each sample was assayed in triplicate, and data are expressed as relative light units (RLU) in 100 ms. The intra-assay coefficients of variation for all assays were 6% to 10%.

Determination of OxPL/ApoB

OxPL and apoB were analyzed on an intention-to-treat basis.

Lipoprotein (a) and ApoB-100 Levels

Plasma Lip(a) levels were measured by a chemiluminescent ELISA with monoclonal antibody LPA4, as described previously.19 LPA4 does not cross-react with plasminogen. ApoB-100 levels were measured by a commercially available kit (Behring) and C-reactive protein (CRP) levels as described previously.5

Statistical Analysis

Because the baseline and week 16 distributions of the OxPL markers were positively skewed, log-transformed values were used in the statistical models and analyses and antilog-transformed for descriptive statistics, yielding geometric means and 95% confidence intervals (CIs) for baseline, week 16, and percent change from baseline to week 16. Inferential analyses included paired-sample t tests for within–treatment group differences in markers at baseline versus week 16 and independent-sample t tests for between–treat-
TABLE 1. Baseline Characteristics of the 2341 Study Subjects

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (n=1190)</th>
<th>Atorvastatin (n=1151)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>64 (11)</td>
<td>65 (11)</td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>796 (67)</td>
<td>752 (65)</td>
</tr>
<tr>
<td>Presenting syndrome, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unstable angina</td>
<td>534 (45)</td>
<td>527 (46)</td>
</tr>
<tr>
<td>Non–Q-wave myocardial infarction, n (%)</td>
<td>656 (55)</td>
<td>624 (54)</td>
</tr>
<tr>
<td>Past myocardial infarction, n (%)</td>
<td>288 (24)</td>
<td>269 (23)</td>
</tr>
<tr>
<td>Previous coronary revascularization, n (%)</td>
<td>131 (11)</td>
<td>109 (9)</td>
</tr>
<tr>
<td>Hyperlipidemia, n (%)</td>
<td>408 (34)</td>
<td>421 (35)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>636 (53)</td>
<td>629 (55)</td>
</tr>
<tr>
<td>Diabetes mellitus type II, n (%)</td>
<td>280 (24)</td>
<td>251 (22)</td>
</tr>
<tr>
<td>Total cholesterol, mean (SD), mg/dL</td>
<td>207 (37)</td>
<td>206 (38)</td>
</tr>
<tr>
<td>LDL cholesterol, mean (SD), mg/dL</td>
<td>125 (33)</td>
<td>124 (34)</td>
</tr>
<tr>
<td>HDL cholesterol, mean (SD), mg/dL</td>
<td>46 (12)</td>
<td>47 (12)</td>
</tr>
<tr>
<td>Triglycerides, mean (SD), mg/dL</td>
<td>186 (93)</td>
<td>182 (86)</td>
</tr>
</tbody>
</table>

Baseline levels of apoB-100, total apoB-OxPL, total apoB-IC, MDA-LDL autoantibodies, and Lp(a) did not differ between groups. The atorvastatin-treated group had a 42% reduction in LDL cholesterol (124±34 to 72±35 mg/dL, P<0.0001), whereas the placebo-treated group had modest increases (124±34 to 135±37 mg/dL, P<0.0001). From baseline to week 16, significant reductions in absolute and relative levels of apoB-100, total apoB-OxPL, and total apoB-IC (both IgG and IgM) were noted in the atorvastatin group compared with the placebo group: apoB-100, −33.0% versus 5.8%; total apoB-OxPL, −29.7% versus −0.2%; total apoB-IC IgG, −29.5% versus 2.1%; and total apoB-IC IgM, −29.2% versus 5.2%.

Effect of Atorvastatin on OxLDL Markers and Lp(a)

Baseline characteristics did not differ significantly between groups (Table 1) or compared with the entire MIRACL population, and there were no significant differences between patients with and without available blood samples for analysis. For the 2442 patients with baseline data, 10.7% had an end point in the atorvastatin group and 12.8% in the placebo group during the 16-week follow-up period. Among the entire MIRACL population, 14.6% suffered a primary end-point event in the atorvastatin group, compared with 17.2% in the placebo group. Thus, the incidence of recurrent events was lower in the present analysis cohort than the entire MIRACL population, but the risk reduction associated with atorvastatin treatment was similar.

Results

Patient Characteristics

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-25.7% versus 13.2%, \( P<0.0001 \) for all comparisons (Table 2 and Figure 2).

In contrast, absolute OxPL/apoB levels increased significantly in the atorvastatin group but actually decreased significantly in the placebo group (Table 2), suggesting that atorvastatin resulted in OxPL enrichment of apoB-100 particles, despite a reduction in total apoB-OxPL levels. In parallel to the rise in OxPL/apoB, Lp(a) levels also increased to a similar extent in response to atorvastatin (Table 2). There was a significant relative increase in OxPL/apoB (9.5% versus -3.9%) and Lp(a) levels (8.8% versus -0.7%, \( P<0.0001 \) for both, Figure 3) in the atorvastatin group compared with the placebo group. Indeed, strong correlations were noted between OxPL/apoB and Lp(a) at baseline (\( r=0.82 \)) and week 16 (\( r=0.85 \), \( P<0.0001 \) for both, Figure 4). Similar correlations were noted for total apoB-OxPL (data not shown). These findings are consistent with our previous observation that the OxPLs recognized by E06 are predominantly associated with Lp(a).13,19

The relative increases in IgG IC/apoB (9.6% versus -1.8%, \( P<0.0001 \)) and IgM IC/apoB (15.4% versus 9.3%, \( P=0.0053 \)) were also higher in the atorvastatin group compared with placebo (Figure 3). The IgG and IgM MDA-LDL autoantibody levels increased equally in both groups (range, 9.1% to 14.4%; \( P<0.0001 \) for both; Figure 3), as has been shown previously in ACS.13 The treatment group difference was significant for IgG (\( P=0.035 \)) but not IgM (\( P=0.16 \)).

Pearson correlations between log-transformed CRP levels and OxLDL markers and Lp(a) at baseline and week 16 were not statistically significant.

**Relationship of Baseline OxLDL Markers and Lp(a) to Clinical Outcomes**

With increasing baseline levels of either total apoB-IC IgM or IC/apoB IgM, there was reduced risk (odds ratio, 0.81 for both) of recurrent events (\( P=0.032 \) and 0.013, respectively; Figure 5). In this analysis, a 1-U increase on the log scale was slightly greater than the interquartile range (the difference between the 25th and 75th percentiles). Baseline levels of other OxLDL markers, LDL-C, apoB-100, or Lp(a), were not predictive of risk at 16 weeks.

**Discussion**

This study reveals that high-dose atorvastatin significantly reduced the total content of OxPL present on all circulating apoB-100 particles and suggests that the early clinical benefit
of atorvastatin in ACS may be mediated in part through a reduction of vasoactive and proinflammatory OxPL in plasma.\textsuperscript{21} Interestingly, on average, individual apoB-100 particles at the new steady state were actually enriched in OxPL (ie, an increased OxPL/apoB ratio), in conjunction with a strikingly similar increase in Lp(a), which we have previously shown binds OxPL.\textsuperscript{13,19,20} Although our observations do not establish a causal mechanism, we hypothesize that with the reduction of LDL cholesterol levels and inflammation,\textsuperscript{22} there ensues a mobilization of OxPL from the vessel wall, transient binding by apoB-100 particles [chiefly Lp(a)], and clearance from the circulation. In addition, these data provide further evidence for a novel physiological and/or pathophysiological role of Lp(a), which we\textsuperscript{13,19} and others\textsuperscript{23} have proposed binds and transports inflammatory OxPL.

It should be appreciated that different antibodies are used to detect oxidation epitopes on OxLDL, and, dependent on the epitope measured, different information may be obtained. We have therefore suggested that authors use the antibody used in their assay in their designation of OxLDL to call attention to this possibility at this early stage of such measurements.\textsuperscript{13} Thus, we designate our measure of OxLDL as OxLDL-E\textsubscript{06} (OxPL/apoB). Because our assay was designed to provide a physical estimate of the OxPL epitope detected by E\textsubscript{06} already normalized for apoB-100 levels, eg, to yield OxPL/apoB, our methodology allows for 2 complementary but unique sets of measurements. First, it quantifies the number of E\textsubscript{06} epitopes per apoB-100 particle (OxPL/apoB), our methodology allows for 2 complementary but unique sets of measurements. First, it quantifies the number of E\textsubscript{06} epitopes per apoB-100 particle (OxPL/apoB), which by design is independent of plasma LDL cholesterol levels.\textsuperscript{13} Second, when the OxPL/apoB is multiplied by (independently measured) plasma apoB-100 levels, one derives total apoB-OxPL levels present on all apoB-100 particles.

The role of statins in reducing plasma OxLDL in ACS has not been described previously. On the basis of the present study, it can be hypothesized that statin-mediated reduction in total plasma levels of OxPL and apoB-IC may occur through both a reduction in the substrate for oxidation (ie, reducing LDL levels and its associated lipids) and possibly through direct anti-inflammatory effects of atorvastatin metabolites, which have potent antioxidant effects.\textsuperscript{24} In vitro studies using several different statins and/or their metabolites demonstrate both a reduction in markers of generalized oxidative stress and LDL susceptibility to oxidation.\textsuperscript{16} For example, in patients with hypercholesterolemia, simvastatin has been shown to reduce the formation of F\textsubscript{2}-isoprostanes and plasma Ox-LDL levels, although the epitope of OxLDL measured in this study was not defined.\textsuperscript{23} Moreover, statins also have other reported pleiotropic effects, at least in animal models, such as nitric oxide–sparing properties.\textsuperscript{9}

OxPLs are known to be highly inflammatory and to induce vasoconstriction,\textsuperscript{21} and it is possible that removal of such OxPLs contributes to rapid improvement in endothelial function. This is supported by several studies showing improvement in coronary\textsuperscript{17} and brachial endothelial function\textsuperscript{16} with LDL apheresis or lovastatin treatment.\textsuperscript{15} More specifically, Tamai et al\textsuperscript{16} have shown that acetylcholine-induced brachial artery vasodilation improves rapidly within 4 hours after LDL apheresis [Lp(a) is also removed], and the best correlate of improvement was reduced plasma OxLDL levels, measured by use of monoclonal antibody DLH3, which binds to an OxPL epitope nearly identical to that bound by E\textsubscript{06}. Penny et al\textsuperscript{15} have shown that OxLDL-E\textsubscript{06} was the best correlate of acetylcholine-induced coronary vasodilation after lovastatin therapy in patients with CAD. LDL apheresis also decreases plasma concentrations of another model OxLDL, MDA-LDL, by 61\%.\textsuperscript{26} A reduction in total OxPL may also produce antithrombotic effects, which, in turn, may be related to clinical benefit of statin treatment.\textsuperscript{22} However, in this and previous studies,\textsuperscript{13} we have not found an association between any plasma OxLDL markers and CRP.

Our analyses also reveal the complementary observation that the plasma apoB particles of atorvastatin-treated patients were enriched in OxPL (an absolute 13.4\% difference compared with placebo), even though there was an overall reduction in the content of total OxPL on all apoB-100 particles. What are the potential mechanisms of the increase in OxPL/apoB plasma levels after treatment with atorvastatin? In human studies, Crisby et al\textsuperscript{27} have shown that 3 months of treatment with pravastatin before carotid endarterectomy markedly reduced OxLDL immunostaining in carotid plaques, using the oxidation-specific antibody NA59, which recognizes 4-hydroxynonenal oxidation-specific epitopes. Tsimikas et al\textsuperscript{18} in an LDLR\textsuperscript{−/−} mouse model and Aikawa et al\textsuperscript{19} in a New Zealand White rabbit model, both using the oxidation-specific antibody MDA2, have shown decreased OxLDL content in aortic plaques after aggressive dietary lipid lowering. Additional unpublished data from both these murine and rabbit experiments, which do not have Lp(a), as well as similar studies with cynomolgus monkeys, which do have Lp(a), show that after regression of established atherosclerosis by diet-induced lipid lowering, there are similar increases in OxPL/apoB plasma levels but markedly diminished total apoB-OxPL levels, similar to the MIRACL study. In all 3 animal studies, a direct immunochemical analysis of the arterial tissue with antibody E\textsubscript{06} demonstrated a marked depletion of OxPL epitopes from the vessel wall, even as the plasma OxPL/apoB ratios were increased from the baseline measurements. Thus, in association with lesion regression, there was a clear net efflux of OxPL from the vessel wall at a time when the OxPL/apoB ratio in plasma was increased (Tsimikas and Witztum, unpublished observations). In addition, unpublished in vitro data in our laboratory show that even in a PBS buffer, there is preferential physical transfer of OxPL (derived from OxLDL) to Lp(a) compared with LDL. These data strongly support the hypothesis that the increase in OxPL/apoB associated with atorvastatin treatment is a surrogate marker of net OxPL efflux from the vessel wall. This hypothesis deserves further study.

Lp(a) levels were also modestly increased in response to atorvastatin in this study, which has previously been observed during the treatment of hypercholesterolemia with other statins\textsuperscript{28–32} but has been underappreciated. One might speculate that increased Lp(a) levels occur in response to the enhanced efflux of OxPL from the vessel wall to facilitate their transport and elimination, although the mechanisms mediating such processes are unknown. In addition, it is also possible that antiinflammatory and antiatherogenic functions of HDL may have been improved by atorvastatin, leading to
increased OxPL efflux.\textsuperscript{33} HDL, and in particular, a pre-\textbeta fraction of HDL, may be the preferred initial acceptor of cholesterol from cellular sources. Recently, Navab et al\textsuperscript{14} have observed that an apoA-I mimetic compound effects efflux of OxPL from cells to such a pre-\textbeta HDL fraction, and we speculate that in turn, Lp(a) will then preferentially accept such OxPL from the pre-\textbeta HDL. This potential mechanism of efflux of OxPL from the vessel wall may be analogous to the rapid effects of apoA-1/phospholipid complexes in reducing coronary atheroma volume, which presumptively also mobilized lipids out of the vessel wall.\textsuperscript{35} In support of this hypothesis is the recent observation that the OxPL/apoB ratio increased, as did Lp(a), in subjects consuming a low-fat diet, another condition in which one might speculate that there was mobilization of OxPL from the artery wall.\textsuperscript{36}

In support of a potential transport function of OxPL by Lp(a), we have recently documented an \textasciitilde 50\% increase in plasma OxLDL-E06 (ie, OxPL/apoB) levels immediately after PCI, presumably released from disrupted plaques, with a simultaneous and similar increase in Lp(a) levels.\textsuperscript{19} Furthermore, the released OxPL epitopes were initially equally present on both apoB-100 and Lp(a) particles but appeared to transfer to Lp(a) nearly exclusively by 6 hours.\textsuperscript{19} In patients presenting with ACS or undergoing PCI,\textsuperscript{13,19} we have also shown a strong association between plasma levels of OxLDL-E06 (OxPL/apoB) and Lp(a), further defining a novel pathophysiological association between OxPL and Lp(a).

It is also possible that Lp(a) contributes directly to the degradation of such OxPL, because Lp(a) was reported to be greatly enriched in plateau-activating factor acetyl hydrolase, an enzyme that can degrade such OxPL.\textsuperscript{21,37} We have previously suggested that this potential physiological function of Lp(a) may be beneficial acutely, particularly in patients with normal Lp(a) levels. However, in patients with chronically elevated levels, Lp(a), with its predilection for enhanced binding to the extracellular matrix of atherosclerotic lesions (reviewed in Tsimikas et al\textsuperscript{13}), may be proinflammatory and proatherogenic because of the enhanced OxPL content.

The highest baseline levels of IgM IC/apoB and total apoB-IC were associated with reduced risk of recurrent events (OR, 0.81 and 0.84, respectively), and there was a similar trend with IgM MDA-LDL autoantibodies (OR, 0.90). Although the underlying mechanisms are unclear, this suggests a potential protective effect of IgM OxLDL autoantibodies, as has been shown in animal models immunized with OxLDL or pneumococcal vaccine (which contains the same epitopes as OxLDL), which induce high circulating levels of OxLDL-specific IgM autoantibodies and decreased atherosclerosis.\textsuperscript{38} This is also consistent with previous studies showing an inverse correlation between IgM OxLDL autoantibody titer and CAD,\textsuperscript{33} hypertension,\textsuperscript{39} and carotid and femoral atherosclerosis.\textsuperscript{40,41}

Limitations of the present study include the absence of blood samples at an intermediate time point during randomized treatment. Had samples been available for such measurements, the change in OxPL markers from baseline to the intermediate time point could have been related to the risk of an event after the intermediate time point. The high correlation of OxLDL-E06 with Lp(a) raises the question of whether measurements of OxLDL-E06 will provide incremental information above and beyond measurement of Lp(a). Additional experimental and appropriately powered clinical studies will be needed to establish whether OxPL markers are useful in predicting clinical outcomes. Nonetheless, our data do suggest novel physiological and/or pathophysiological functions of Lp(a) that warrant further investigation in future studies.

In conclusion, this study shows that atorvastatin therapy, compared with placebo, results in marked reduction in total plasma OxPL associated with apoB-100, while at the same time enlarging a pool of Lp(a) particles enriched in OxPL. These observations support the hypothesis that early atorvastatin treatment after ACS enhances mobilization and subsequent clearance of OxPL from the arterial wall, a mechanism that may contribute to the clinical benefit of statin therapy.

Acknowledgments

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References


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