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Comparison Effect of Atorvastatin (10 versus 80 mg) on Biomarkers of Inflammation and Oxidative Stress in Subjects With Metabolic Syndrome

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Abstract

Metabolic syndrome (MS), characterized by low-grade inflammation, confers an increased risk for cardiovascular disease. Statins, in addition to having lipid-lowering effects, have pleiotropic effects and decrease biomarkers of inflammation and oxidative stress. The Treating to New Target Study showed a greater decrease in low-density lipoprotein (LDL) cholesterol and cardiovascular events with atorvastatin 80 mg versus 10 mg in patients with MS with coronary heart disease. However, part of this benefit could be caused by the greater pleiotropic effects of the higher dose of atorvastatin. The dose–response effect of atorvastatin on biomarkers of inflammation and oxidative stress has not been investigated in subjects with MS. Thus, the dose–response effect of atorvastatin on biomarkers of inflammation (high-sensitivity C-reactive protein [hs-CRP], matrix metalloproteinase-9, and nuclear factor- κ B [NF- κ B] activity) and oxidative stress (oxidized LDL, urinary nitrotyrosine, F2-isoprostanes, and monocyte superoxide release) was tested in a randomized double-blind clinical trial in subjects with MS. Seventy subjects were randomly assigned to receive placebo or atorvastatin 10 or 80 mg/day for 12 weeks. A strong dose–response (atorvastatin 10 compared with 80 mg, $p < 0.05$) was observed for changes in total, LDL (32% and 44% reduction), non–high-density lipoprotein (28% and 40% reduction), and oxidized LDL cholesterol (24% and 39% reduction) at atorvastatin 10 and 80 mg, respectively. Hs-CRP, matrix metalloproteinase-9, and NF- κ B significantly decreased in the 80-mg atorvastatin group compared with baseline. In conclusion, this randomized trial of subjects with MS showed the superiority of atorvastatin 80 mg compared with its 10-mg dose in decreasing oxidized LDL, hs-CRP, matrix metalloproteinase-9, and NF- κ B activity.

Numerous studies reported that statins reduced cardiovascular events as a result of their beneficial effects on lipids and other pleiotropic anti-inflammatory effects.^{1–3} Tsimikas et al⁴ reported that statins promoted potent systemic anti-oxidant effects through specific inflammatory pathways. In the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering trial, high-dose atorvastatin (80 mg/day for 16 weeks) versus placebo reduced total plasma levels of oxidized phospholipids and immune complexes present on apolipoprotein B-100 in patients with acute coronary syndromes. Furthermore, in the Reversal of Atherosclerosis with Aggressive Lipid Lowering study,⁵ plaque progression in patients with coronary artery disease was reported to be attenuated using an intensive, but not moderate, lipid-lowering strategy with either atorvastatin or pravastatin. The Treating to New Target Study carried out in patients with coronary heart disease and metabolic syndrome (MS) found

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an incremental benefit of high-dose atorvastatin compared with low-dose atorvastatin on reduction of low-density lipoprotein (LDL) cholesterol and cardiovascular events,⁶ possibly because of the greater pleiotropic effects of a high dose of atorvastatin. The dose-response effect of atorvastatin on biomarkers of inflammation and oxidative stress in patients with MS has not been investigated. Thus, we tested the dose-response effect of atorvastatin on various biomarkers of inflammation and oxidative stress in subjects with MS.

Methods

This study was approved by the Institutional Review Boards of University of California, Davis Medical Center, and the Department of Veterans Affairs Northern California Health Care System. All subjects gave informed consent. This was a randomized double-blind placebo-controlled study of subjects with MS. Exclusion criteria were smoking; use of lipid-lowering drugs; diabetes; aspirin therapy (>81 mg/day); anti-inflammatory drugs; infection; cancer; recent major surgery; illness; liver, renal, or uncompensated metabolic/hormonal disorders; and high-sensitivity C-reactive protein (hs-CRP) >10 mg/L from the blood test at the screening visit, suggestive of overt inflammation. MS was defined using the criteria of the National Cholesterol Education Program Adult Treatment Panel III,⁷ and the subjects eligible for the study had to meet ≥ 3 features for the diagnosis.

At the baseline visit, subjects were randomly assigned to 1 of the 3 groups of placebo (0 mg) or 10 or 80 mg/day of atorvastatin for 12 weeks. A total of 70 subjects (n = 24, 23, and 23 for placebo and atorvastatin 10 or 80 mg, respectively) completed the study. A fasting blood specimen was obtained at baseline and at the end of a 12-week period in each group for measurement of lipid profile, hs-CRP, isolation of monocytes (for superoxide anion release and cytokines), and other parameters of inflammation, as well as oxidative stress. At baseline and end of the study, a first morning urine sample was also collected for measurement of urinary isoprostanes and nitrotyrosine. All routine chemistry tests, including hs-CRP at the screening visit, were conducted using standard laboratory techniques in the Clinical Pathology Laboratory. However, CRP measurement at baseline and 12 weeks was performed in a single assay using an enzyme-linked immunosorbent assay kit (Alpco Diagnostic, Salem, New Hampshire). Each sample was assayed in duplicate. The intra-assay coefficient of variation for this assay was <5%. At the 6-week period, subjects were tested for liver chemistry safety parameters (measurement of aspartate and alanine aminotransferases). Any subject with liver chemistry test results >2 times the upper limit of normal was discontinued from the study. One subject in the 80-mg group developed increased liver chemistry test values at the 6-week period and was discontinued from the study. Another subject developed increased liver chemistry test values at the 12-week period. Both subjects had normal liver chemistry test values at the 2-week follow-up visit.

Mononuclear cells were isolated from 30 ml of fasting heparinized blood using Ficoll-Hypaque gradient (Sigma Chemical Company, St. Louis, Missouri), followed by monocyte isolation using magnetic cell sorting with the depletion technique (Miltenyi Biotech, Auburn, California) as described.² Isolated monocytes were used for the measurement of superoxide release using acetylated cytochrome C, as reported previously.² Monocytes were activated with lipopolysaccharide (100 ng/ml) at 37°C. The release of cytokines (interleukin-6 and tumor necrosis factor- α) was assayed in supernatants of lipopolysaccharide-activated monocytes after an overnight incubation at 37°C using enzyme-linked immunosorbent assay kits from BioSource Int. (Carlsbad, California) and R&D Systems (Minneapolis, Minnesota), respectively. The coefficient of variation of these assays was <10%. Cytokine secretion from monocytes was expressed as nanograms per milligram of cell protein.

Oxidized LDL was measured using a solid-phase 2-site enzyme immunoassay (Mercodia, Uppsala, Sweden) using the capture antibody, monoclonal antibody-4E6. Urinary nitrotyrosine (Chemicon Int., Inc., Billerica, Massachusetts), isoprostanes (Oxis Int., Inc., Foster City, California), soluble cluster of differentiation 40-ligand (sCD40L), and matrix metalloproteinase-9 (R&D Systems, Minneapolis, Minnesota) were measured using enzyme-linked immunosorbent assay kits. Values for nitrotyrosine and isoprostanes were normalized per milligram of creatinine measured in urine. Activation of nuclear factor- κ B (NF- κ B) binding to the nucleus of monocytes was determined using the nonradioactive Trans AM-NF κ B p65 transcription factor assay (Active Motif, Carlsbad, California) using nuclear extracts following the manufacturer's instructions. Intra- and interassay coefficients of variation for these assays were <8%.

Data were expressed as mean $\pm$ SD for parametric data and median and 25th to 75th percentiles for nonparametric data. Statistical analysis was performed using Statistical Analysis System software (SAS Institute, Cary, North Carolina). After repeated-measures analysis of variance, baseline and posttreatment differences between groups were assessed using Mann-Whitney (Monte Carlo 2-tailed estimate) tests. Percentage of change and delta differences between groups were compared using Wilcoxon's signed-rank tests.

Results

There were no significant differences in various characteristics among the 3 groups at the baseline visit (Table 1). A strong dose-response was observed for atorvastatin therapy, showing a significant decrease in total (4%, 22%, and 34% in placebo and atorvastatin 10 and 80 mg, respectively) and LDL cholesterol (3%, 32%, and 44% in placebo and atorvastatin 10 and 80 mg, respectively), with $p < 0.005$ by analysis of variance for trend (Table 2). Furthermore, non-high-density lipoprotein cholesterol also decreased significantly ($p < 0.005$) compared with baseline and placebo in the 10- and 80-mg groups (Table 2). There was a significant ($p < 0.05$) difference for decrease in total, LDL, and non-high-density lipoprotein cholesterol in the 10-mg compared with the 80-mg atorvastatin group. However, there was no significant difference in high-density lipoprotein cholesterol in all 3 groups compared with baseline, although triglycerides decreased significantly ($p < 0.02$) in the 80-mg group compared with baseline values (Table 2).

The primary study end point was change in hs-CRP by atorvastatin dose. In contrast to lipid-related response at 12 weeks, hs-CRP significantly ($p < 0.01$) decreased only with atorvastatin 80 mg/day compared with baseline values. There was no significant decrease in hs-CRP with atorvastatin 10 mg/day (Table 3).

Matrix metalloproteinase-9 and monocytic NF- κ B activity significantly ($p < 0.05$) decreased in the 80-mg group compared with baseline values, with no change in the 10-mg or placebo groups (Table 3). However, sCD40L and lipopo-lysaccharide-activated monocytic release of cytokines were not affected after either dose of atorvastatin compared with baseline and placebo (Table 3).

Oxidized LDL showed significant and dose-dependent inhibition ($p = 0.03$ for 10 compared with 80 mg) with atorvastatin therapy. However, there were no significant differences in urinary nitrotyrosine, F2-isoprostanes, and monocyte superoxide release in either group of atorvastatin therapy compared with either placebo or baseline (Table 4).

Discussion

We previously showed in a prospective, randomized, double-blind, crossover trial¹ of combined hyperlipidemic patients that the decrease in CRP with statins was a class effect. This

has now been confirmed by numerous investigators in patients with coronary artery disease, diabetes mellitus, and hypercholesterolemia.^{8–13}

Deedwania et al⁶ reported an incremental benefit of intensive lipid therapy with atorvastatin 80 mg on the decrease in LDL cholesterol and cardiovascular events compared with a 10-mg dose. However, there is a paucity of information about the dose–response effects of atorvastatin examining biomarkers of inflammation and oxidative stress in subjects with MS. In the present double-blind placebo-controlled study, we reported that atorvastatin (10 and 80 mg/day) in subjects with MS dose dependently decreased total, LDL, and oxidized LDL cholesterol. Importantly, non–high-density lipoprotein cholesterol is a target of treatment in patients with MS, which significantly decreased to <130 mg/dl in 65% and 87% of subjects in the atorvastatin 10- and 80-mg groups in the present study, respectively. Pleiotropic effects, evidenced by a decrease in such inflammatory markers as hs-CRP and matrix metalloproteinase-9, were evident in the high-dose atorvastatin group only. Low-dose atorvastatin failed to show pleiotropic effects in our subject population. Earlier, Kinlay et al³ showed a significant decrease in hs-CRP with high-dose atorvastatin (80 mg/day for 16 weeks) compared with placebo in patients with acute coronary syndromes in the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering Study. However, in our study, hs-CRP did not significantly decrease compared with placebo, but significantly decreased compared with baseline in the 80-mg atorvastatin group. Also, Ozaki et al¹³ reported a significant decrease in hs-CRP with atorvastatin 10 mg/day for 6 months in patients with hypercholesterolemia. We speculate that the patient population selected for these studies might have had a higher inflammatory burden at baseline and thus might have benefited more compared with the subject population of our study.

NF- κ B is an important transcription factor in the regulation of inflammatory process,¹⁴ reported to increase in patients with diabetes¹⁵ and obesity.¹⁶ Because statins were previously shown to downregulate NF- κ B activity,¹⁷ we showed in human monocytes that atorvastatin therapy significantly decreased NF- κ B activity compared with baseline. Thus, we extended the reported important observation that statins downregulated mononuclear cell NF- κ B activity, consistent with an earlier report from our group in subjects with MS treated with simvastatin therapy.² Furthermore, matrix metalloproteinase-9 increased in patients with acute coronary syndrome^{18,19} and showed a strong correlation with high CRP. Importantly, a pleiotropic effect of statins appears to be associated with modulation of matrix metalloproteinase activation.²⁰ Here, we report significant decreases in matrix metalloproteinase-9 in the atorvastatin 80-mg group. Furthermore, sCD40L is predominantly released from activated platelets and was shown to increase in patients with atherosclerotic disease. Although some investigators^{21,22} earlier reported a significant decrease in sCD40L with a low dose of atorvastatin in hypercholesterolemic patients, our study did not show a significant decrease in sCD40L with atorvastatin therapy. Because NF- κ B^{23,24} is known to drive matrix metalloproteinase-9 and hs-CRP, it is pertinent that atorvastatin 80 mg resulted in a significant decrease in these closely related parameters.

Increased oxidized LDL in the vessel wall and circulation was present in patients with acute coronary syndrome²⁵ and was associated with endothelial dysfunction.²⁶ Also, subjects with MS showed increased plasma oxidized LDL.²⁷ Furthermore, atorvastatin at a higher dose (80 mg/day for 16 weeks) was reported to decrease plasma oxidized LDL in the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering trial.⁴ Our study extended these results by showing that atorvastatin therapy had a dose–response effect for decreasing oxidized LDL and thus had potent antioxidant effects.²⁸

We also examined other markers of oxidative stress, such as urinary nitrotyrosine, F2-isoprostanes, and monocyte superoxide release. Our study did not show a significant effect on

these measures. Although Shishehbor et al^{29,30} earlier reported a significant decrease in plasma nitrotyrosine with atorvastatin therapy (10 mg/day for 12 weeks), both these studies^{29,30} were not placebo controlled, and circulating tyrosine-modified proteins were measured. We cannot comment on the differences in results between these studies because their sample source was different, plasma as opposed to urine in our study. However, we believe urinary measurement of nitrotyrosine is a valid measure of oxidative stress. Furthermore, data were scanty in reports of urinary F2-isoprostanes in subjects with MS. Overall, our study suggested that atorvastatin did not have antioxidative effects in subjects with MS with regard to nitrotyrosine, isoprostanes, or superoxide radical production.

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References

1. Jialal I, Stein D, Balis D, Grundy SM, Adams-Huet B, Devaraj S. Effect of hydroxymethyl glutaryl coenzyme A reductase inhibitor therapy on high sensitive C-reactive protein levels. *Circulation* 2001;103:1933–1935. [PubMed: 11306519]
2. Devaraj S, Chan E, Jialal I. Direct demonstration of an anti-inflammatory effect of simvastatin in subjects with the metabolic syndrome. *J Clin Endocrinol Metab* 2006;91:4489–4896. [PubMed: 16968805]
3. Kinlay S, Schwartz GG, Olsson AG, Rifai N, Leslie SJ, Sasiela WJ, Szarek M, Libby P, Ganz P. Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering Study Investigators. High-dose atorvastatin enhances the decline in inflammatory markers in patients with acute coronary syndromes in the MIRACL Study. *Circulation* 2003;108:1560–1566. [PubMed: 12975259]
4. Tsimikas S, Witztum JL, Miller ER, Sasiela WJ, Szarek M, Olsson AG, Schwartz GG. Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) Study Investigators. 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. *Circulation* 2004;110:1406–1412. [PubMed: 15353498]
5. Nicholls SJ, Tuzcu EM, Sipahi I, Schoenhagen P, Hazen SL, Ntanios F, Wun CC, Nissen SE. Effects of obesity on lipid-lowering, anti-inflammatory, and antiatherosclerotic benefits of atorvastatin or pravastatin in patients with coronary artery disease (from the REVERSAL Study). *Am J Cardiol* 2006;97:1553–1537. [PubMed: 16728212]
6. Deedwania P, Barter P, Carmena R, Fruchart JC, Grundy SM, Haffner S, Kastelein JJ, LaRosa JC, Schachner H, Shepherd J, Waters DD. Treating to New Targets Investigators. Reduction of low-density lipoprotein cholesterol in patients with coronary heart disease and metabolic syndrome: analysis of the Treating to New Targets Study. *Lancet* 2006;368:919–928. [PubMed: 16962881]
7. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* 2001;285:2486–2497. [PubMed: 11368702]
8. Liao JK. Role of statin pleiotropism in acute coronary syndromes and stroke. *Int J Clin Pract Suppl* 2003;134:S51–S57.
9. Rosenson RS, Tangney CC. Antiatherothrombotic properties of statins: implications for cardiovascular event reduction. *JAMA* 1998;279:1643–1650. [PubMed: 9613915]
10. Waehre T, Damas JK, Gullestad L, Holm AM, Pedersen TR, Arnesen KE, Torsvik H, Froland SS, Semb AG, Aukrust P. Hydroxymethyl glutaryl coenzyme A reductase inhibitors down-regulate chemokines and chemokine receptors in subjects with coronary artery disease. *J Am Coll Cardiol* 2003;41:1460–1467. [PubMed: 12742282]

11. Waehre T, Yndestad A, Smith C, Haug T, Tunheim SH, Gullestad L, Froland SS, Semb AG, Aukrust P, Damas JK. Increased expression of IL-1 in coronary artery disease with downregulatory effects of HMG-CoA reductase inhibitors. *Circulation* 2004;109:1966–1972. [PubMed: 15051633]
12. Meredith KG, Horne BD, Pearson RR, Maycock CA, Lappe DL, Anderson JL, Muhlestein JB. Comparison of effects of high (80 mg) versus low (20 mg) dose of simvastatin on C-reactive protein and lipoproteins in patients with angiographic evidence of coronary arterial narrowing. *Am J Cardiol* 2007;99:149–153. [PubMed: 17223409]
13. Ozaki K, Kubo T, Imaki R, Shinagawa H, Fukaya H, Ohtaki K, Ozaki S, Izumi T, Aizawa Y. The anti-atherosclerotic effects of lipid lowering with atorvastatin in patients with hypercholesterolemia. *J Athero-scler Thromb* 2006;13:216–219.
14. de Winther MP, Kanters E, Kraal G, Hofker MH. Nuclear factor kappa B signaling in atherogenesis. *Arterioscler Thromb Vasc Biol* 2005;25:904–914. [PubMed: 15731497]
15. Bierhaus A, Schiekofer S, Schwaninger M, Andrassy M, Humpert PM, Chen J, Hong M, Luther T, Henle T, Klötting I, et al. Diabetes-associated sustained activation of the transcription factor nuclear factor kappa B. *Diabetes* 2001;50:2792–2808. [PubMed: 11723063]
16. Ghanim H, Aljada A, Hofmeyer D, Syed T, Mohanty P, Dandona P. Circulating mononuclear cells in the obese are in a proinflammatory state. *Circulation* 2004;110:1564–1571. [PubMed: 15364812]
17. Hilgendorff A, Muth H, Parviz B, Staubitz A, Haberbosch W, Tillmanns H, Holschermann H. Statins differ in their ability to block NF kappa B activation in human blood monocytes. *Int J Clin Pharmacol Ther* 2003;41:397–401. [PubMed: 14518599]
18. Zeng B, Prasan A, Fung KC, Solanki V, Bruce D, Freedman SB, Brieger D. Elevated circulating levels of matrix metalloproteinase-9 and -2 in patients with symptomatic coronary artery disease. *Int Med J* 2005;35:331–335.
19. Fukuda DK, Shimada A, Tanaka T, Kusuyama H, Yamashita S, Ehara Y, Nakamura T, Kawarabayashi H, Yoshikawa J. Comparison of levels of serum MMP-9 in patients with acute myocardial infarction versus unstable angina pectoris versus stable angina pectoris. *Am J Cardiol* 2006;97:175–180. [PubMed: 16442358]
20. Yasuda S, Miyazaki S, Kinoshita H, Nagaya N, Kanda M, Goto Y, Nonogi H. Enhanced cardiac production of matrix metalloproteinase-2 and -9 and its attenuation associated with pravastatin treatment in patients with acute myocardial infarction. *Clin Sci (Lond)* 2007;112:43–49. [PubMed: 16939410]
21. Alber HF, Frick M, Suessenbacher A, Doerler J, Schirmer M, Stocker EM, Dichtl W, Pachinger O, Weidinger F. Effect of atorvastatin on circulating proinflammatory T-lymphocyte subsets and soluble CD40 ligand in patients with stable coronary artery disease—a randomized, placebo-controlled study. *Am Heart J* 2006;151:139–142. [PubMed: 16368305]
22. Chu CS, Lee KT, Lee MY, Su HM, Voon WC, Sheu SH, Lai WT. Effects of atorvastatin and atorvastatin withdrawal on soluble CD40L and adipocytokines in patients with hypercholesterolaemia. *Acta Cardiol* 2006;61:263–269. [PubMed: 16869445]
23. Liuzzo GM, Santamaria LM, Biasucci M, Narducci V, Colafrancesco A, Porto S, Brugaletta M, Pinnelli V, Rizzello A, Crea F. Persistent activation of nuclear factor kappa-B signaling pathway in patients with unstable angina and elevated levels of C-reactive protein: evidence for a direct proinflammatory effect of azide and LPS-free C-reactive protein on human monocytes via nuclear factor kappa-B activation. *J Am Coll Cardiol* 2007;49:185–194. [PubMed: 17222729]
24. Verma S, Devaraj S, Jialal I. Is C-reactive protein an innocent bystander or proatherogenic culprit? C-Reactive protein promotes athero-thrombosis. *Circulation* 2006;113:2135–2150. [PubMed: 16671184]
25. Ehara S, Ueda M, Naruko T. Elevated levels of oxidized low-density lipoprotein show a positive relationship with the severity of acute coronary syndromes. *Circulation* 2001;103:1955–1960. [PubMed: 11306523]
26. Penny WF, Ben Yehuda O, Kuroe K, Long J, Bond A, Bhargava V, Peterson JF, McDaniel M, Juliano J, Witztum JL, Ross J Jr, Peterson KL. Improvement of coronary artery endothelial dysfunction with lipid-lowering therapy: heterogeneity of segmental response and correlation with plasma-oxidized low density lipoprotein. *J Am Coll Cardiol* 2001;37:766–774. [PubMed: 11693750]

27. Holvoet P, Kritchevsky SB, Tracy RP, Mertens A, Rubin SM, Butler J, Goodpaster B, Harris TB. The metabolic syndrome, circulating oxidized LDL, and risk of myocardial infarction in well-functioning elderly people in the Health, Aging, and Body Composition Cohort. *Diabetes* 2004;53:1068–1073. [PubMed: 15047623]
28. Aviram, M.; Rosenblat, M.; Bisgaier, CL. Atorvastatin and gemfibrozil metabolites, but not the parent drugs, are potent antioxidants against lipoprotein oxidation; *Atherosclerosis*. 1998. p. 271-280.[http://circ.ahajournals.org/cgi/external_ref?access_num=10.1016/S0021-9150\(98\)00055-0&link_type=DOI](http://circ.ahajournals.org/cgi/external_ref?access_num=10.1016/S0021-9150(98)00055-0&link_type=DOI)
29. Shishehbor MH, Brennan ML, Aviles RJ, Fu X, Penn MS, Sprecher DL, Hazen SL. Statins promote potent systemic antioxidant effects through specific inflammatory pathways. *Circulation* 2003;108:426–431. [PubMed: 12860913]
30. Shishehbor MH, Aviles RJ, Brennan ML, Fu X, Goormastic M, Pearce GL, Gokce N, Keaney JF Jr, Penn MS, Sprecher DL, Vita JA, Hazen SL. Association of nitrotyrosine levels with cardiovascular disease and modulation by statin therapy. *JAMA* 2003;289:1675–1680. [PubMed: 12672736]

Table 1

Baseline characteristics of the enrolled subjects

Variable	Placebo	Atorvastatin (10 mg/d)	Atorvastatin (80 mg/d)
Age (yrs)	51 ± 12	51 ± 11	50 ± 11
Men/women	12/12	10/13	11/12
Body mass index (kg/m ²)	36 ± 8	37 ± 8	37 ± 8
Systolic blood pressure (mm Hg)	131 ± 18	131 ± 16	132 ± 13
Diastolic blood pressure (mm Hg)	84 ± 89	84 ± 9	87 ± 11
Glucose (mg/dl)	98 ± 32	105 ± 45	102 ± 15
Total cholesterol (mg/dl)	203 ± 24	207 ± 26	211 ± 26
Total triglycerides (mg/dl)	129 (91–156)	121 (100–190)	167 (105–218)
High-density lipoprotein cholesterol (mg/dl)	38 ± 8	40 ± 9	37 ± 7
LDL cholesterol (mg/dl)	138 ± 22	136 ± 26	141 ± 25
hs-CRP (mg/L)	3.5 ± 1.5	4.2 ± 2.4	4.2 ± 1.7
	3.7 (2.1–4.6)	4.1 (2.3–5.9)	3.7 (2.9–5.3)

Data expressed as mean ± SD or median (25th to 75th percentile).

Table 2
Dose-response of atorvastatin on lipid profile in subjects with metabolic syndrome

Variable	Atorvastatin					
	Placebo		10 mg/d		80 mg/d	
	Baseline	Week 12	Baseline	Week 12	Baseline	Week 12
Total cholesterol (mg/dl)	203 ± 24	198 ± 28	207 ± 26	161 ± 35 [*]	211 ± 26	139 ± 33 ^{*†}
LDL cholesterol (mg/dl)	138 ± 22	135 ± 24	136 ± 26	93 ± 27 [*]	141 ± 25	79 ± 27 ^{*†}
High-density lipoprotein cholesterol (mg/dl)	38 ± 8	38 ± 10	40 ± 9	40 ± 10	37 ± 7	36 ± 7
Non-high-density lipoprotein cholesterol (mg/dl)	165 ± 23	167 ± 28	167 ± 29	121 ± 36 [*]	174 ± 26	103 ± 32 ^{*†}
Triglycerides (mg/dl)	129 (91–156)	122 (73–166)	121 (100–190)	99 (77–157)	167 (105–218)	103 [‡] (94–151)

Data expressed as mean ± SD or median (25th to 75th percentile).

^{*}

p < 0.005 compared with baseline and placebo.

[†]

p < 0.05 compared with atorvastatin 10 mg/day.

[‡]

p < 0.02 compared with baseline.

Table 3

Effect of atorvastatin on high-sensitivity C-reactive protein (hs-CRP) and other biomarkers of inflammation in subjects with metabolic syndrome

Variable	Atorvastatin					
	Placebo		10 mg/d		80 mg/d	
	Baseline	Week 12	Baseline	Week 12	Baseline	Week 12
hs-CRP (mg/L)	3.7 (2.1–4.6)	2.3 (1.7–3.7)	4.1 (2.3–5.9)	3.4 (1.9–4.8)	3.7 (2.9–5.3)	2.2* (1.9–3.1)
Matrix metalloproteinase-9 (ng/ml)	11 ± 6	2 ± 6	12 ± 5	10 ± 6	13 ± 6	9 ± 6 [†]
NF-κB (ng/mg protein)	43 ± 26	38 ± 20	45 ± 27	37 ± 24	44 ± 33	28 ± 23 [†]
sCD40L (ng/ml)	1.0 ± 0.9	0.8 ± 0.8	1.1 ± 1.0	1.2 ± 1.4	1.1 ± 1.0	1.2 ± 1.4
Monocyte cytokines (ng/mg protein)	233 ± 250	342 ± 373	329 ± 274	273 ± 324	428 ± 432	323 ± 288
Interleukin-6						
Tumor necrosis factor-α	27 ± 39	28 ± 49	26 ± 33	29 ± 31	31 ± 29	24 ± 27

Data expressed as mean ± SD or median (25th to 75th percentile).

* p < 0.01 compared with baseline.

[†] p < 0.05 compared with baseline.

Table 4
Effect of atorvastatin on biomarkers of oxidative stress in subjects with metabolic syndrome

Variable	Atorvastatin			
	Placebo		10 mg/d	
	Baseline	Week 12	Baseline	Week 12
Oxidized LDL (IU/L)	48 ± 15	51 ± 12	56 ± 19	42 ± 17 ^{*†}
Urinary nitrotyrosine (μmol/mg creatine)	15 ± 10	16 ± 15	14 ± 12	12 ± 5ns
Urinary-F ₂ isoprostanes (pg/mg creatine)	750 ± 380	670 ± 444	893 ± 439	863 ± 530ns
Monocyte superoxide release (nmol/min/mg protein)	1.7 ± 2.3	1.7 ± 1.8	1.2 ± 1.0	1.1 ± 0.9ns
			1.3 ± 1.4	1.1 ± 0.8ns

Data expressed as mean ± SD.

^{*} p < 0.02 compared with baseline.

[†] p < 0.044 compared with placebo.

[#] p < 0.001 compared with baseline and placebo.

[§] p < 0.03 compared with atorvastatin 10 mg/day.

ns = not significant.