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Oxidized Low Density Lipoprotein, Statin Therapy and Carotid Stenosis

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1. Introduction

1.1 Carotid stenosis and atheromatous process

Carotid artery stenosis due to atherosclerosis is a major complication of hyperlipidemia, diabetes mellitus and hypertension. Moreover, the extent of carotid intima media thickness is a measure of atheromatosis and therefore of cardiovascular disease (CVD).

The effect of cholesterol in the process of atheromatosis is now well established. High levels of total cholesterol (TC), as well as of low-density lipoprotein (LDL), very low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), lipoprotein a (Lp-α), and triglycerides (TG), coupled with decreased levels of high-density lipoprotein (HDL) are responsible for the creation of atheromatous plaques (Assmann & Schulte, 1992; Hokanson & Autsin, 1996; Katsouras et al., 2001). Of the above factors, LDL cholesterol, and especially the oxidized LDL (oxLDL) is considered as the most important contributor of atheromatosis (Anderson et al., 1996).

The atheromatous process is completed in the following three stages:

1. In the first stage, LDL cholesterol enters the vessel wall, binds to glucosaminoglucanes, which are part of the extracellular matrix of the intima. This binding is facilitated by apolipoprotein B-100 (ApoB–100). The accumulation of LDL in the vessel wall contributes to the formation of fatty strikes. Following adhesion to the vessel wall, LDL undergoes oxidation by free radicals produced locally, the molecule is altered and chemokines are produced by adjacent vessel wall cells, such as monocyte chemoattractant protein-1 (MCP–1), together with growth factors, which are responsible for the accumulation of monocytes and macrophages. The latter cause further oxidation of LDL, resulting in negative charge, recognition by scavenger receptors located on macrophage membrane and increased uptake of LDL inside the macrophages, as these receptors are not inhibited by increased intracellular concentration of cholesterol. The final result is an enormous accumulation of LDL in the macrophages, which are transformed to foam cells. These cells represent the first step in the atheromatous process (Durrington & Sinderman, 2002) (figure 1).
2. During the second stage, the atheromatous plaque is formed. Foam cells produce growth factors and together with oxLDL result to the attraction of smooth muscle cells.

The latter are then differentiated to fibroblasts and start producing collagen. This collagen covers foam cells, which either are destroyed or are forced to apoptosis. The final result is the formation of a pool of extracellular cholesterol trapped under a fibrous capsid (figure 2). The part which is close to the yet intact vessel wall is the active site of the plaque, where the foam cells are produced. As the plaque extents to the inner layers of the vessel wall, the point of foam cell formation becomes instable and may cause rapture of the plaque (Durrington & Sinderman, 2002) (figure 3).

3. In the third stage, that of the complicated lesion, the rapture of the fibrous capsid of the atheromatous plaque leads to massive evacuation of the cholesterol reservoir. The artery may occult due to the accumulation of platelets and subsequent clotting, leading to acute ischemia or infarction (figure 4). If not so, then the plaque will be further enlarged (Durrington & Sinderman, 2002).
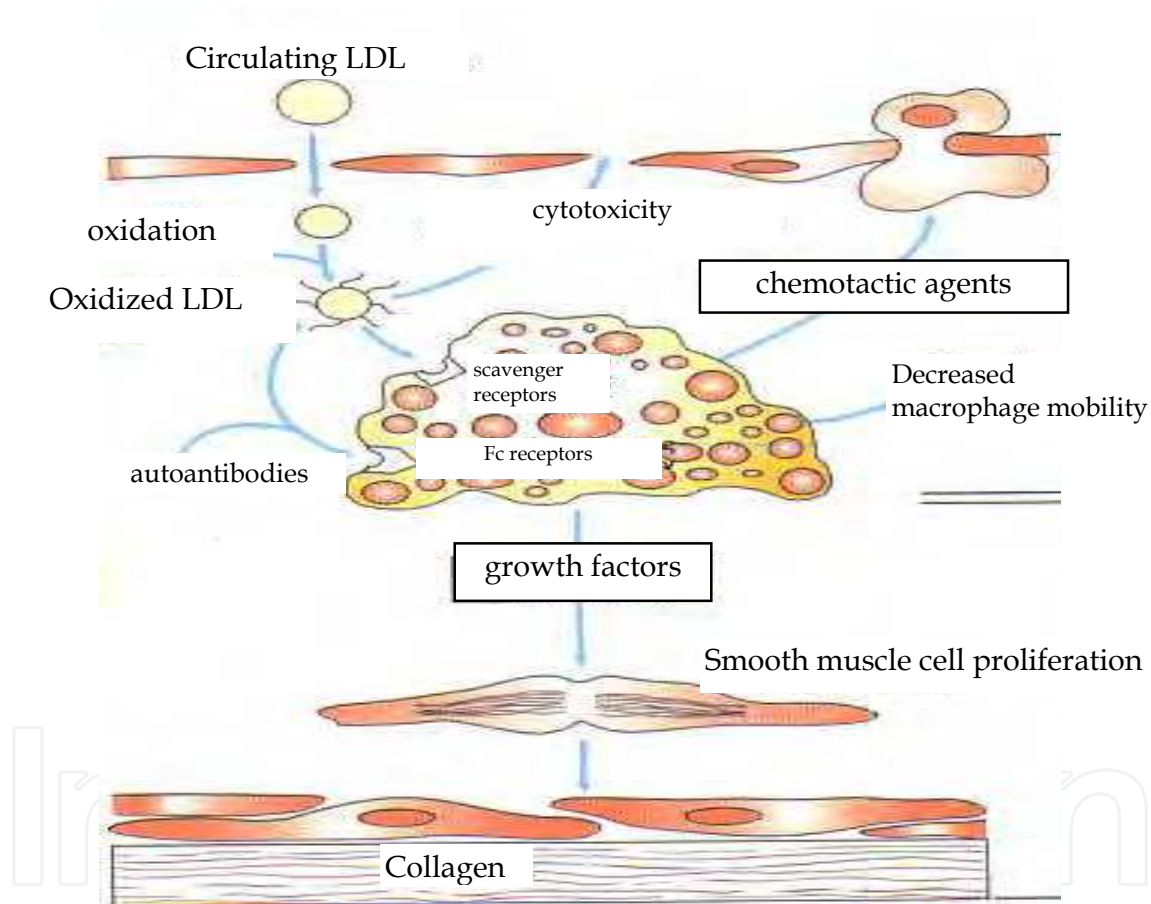

Fig. 1. Atherogenesis. Fatty strikes are characterized by macrophages containing an excess of lipids (foam cells). Foam cells are derived by blood monocytes which are attracted to vessel intima and start phagocytosing lipoproteins, such as oxLDL. The conversion of fatty strike to atheroma depends on proliferation and differentiation of smooth muscle cells to fibroblasts. The latter produce collagen resulting in intima thickening. As the lesion extents further, foam cells are destroyed releasing large amounts of cholesterol trapped in a fibrous capsid. The active site of atheroma is the point which is adjacent to normal endothelium, where foam cells are formed (adopted with persmission from Durrington & Sinderman, 2002).

Avoiding the formation and the instability of the atheromatous plaque is top priority for patients at risk for cardiovascular events. Statins may contribute towards this direction (Corti et al., 2002; Nissen et al., 2004)
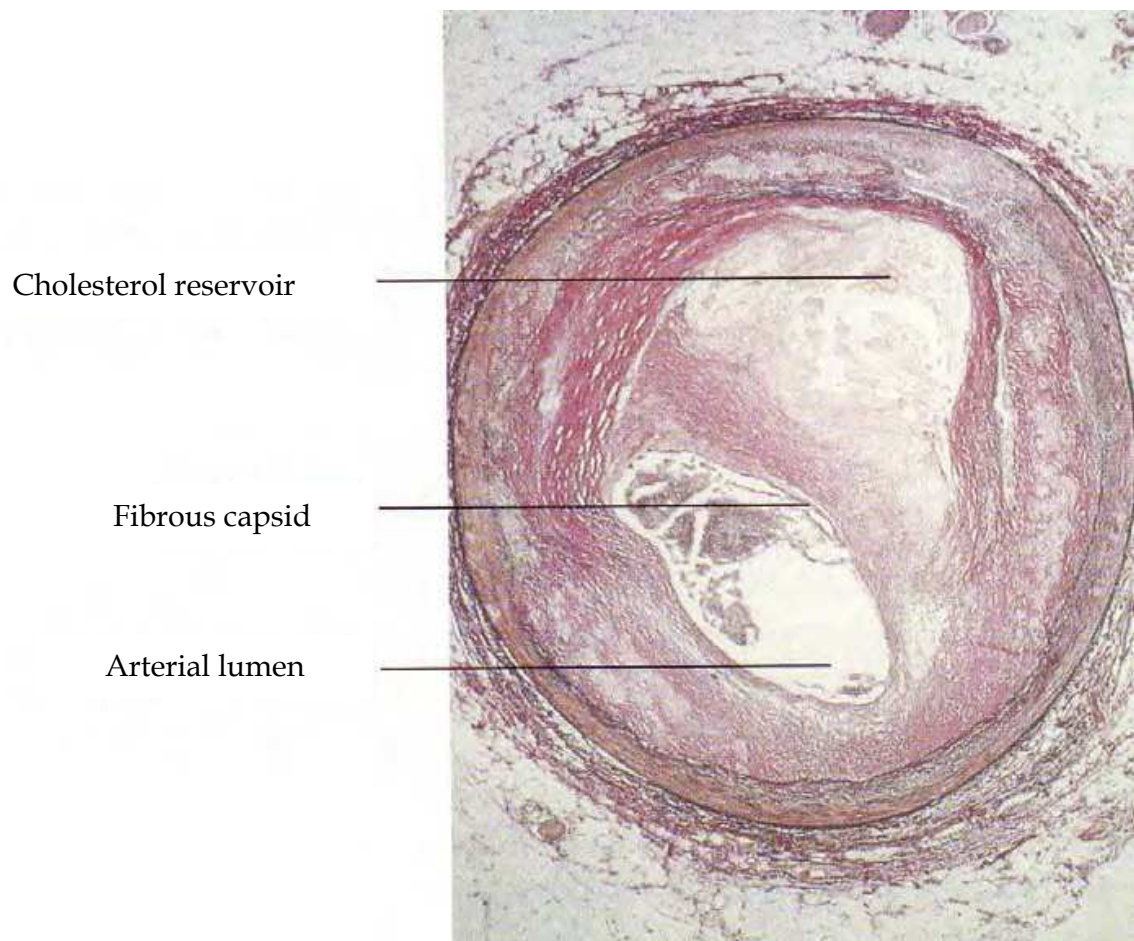

Fig. 2. Advanced atheromatous plaque causing arterial lumen occlusion of 70% (adopted from Durrington & Sinderman, 2002).
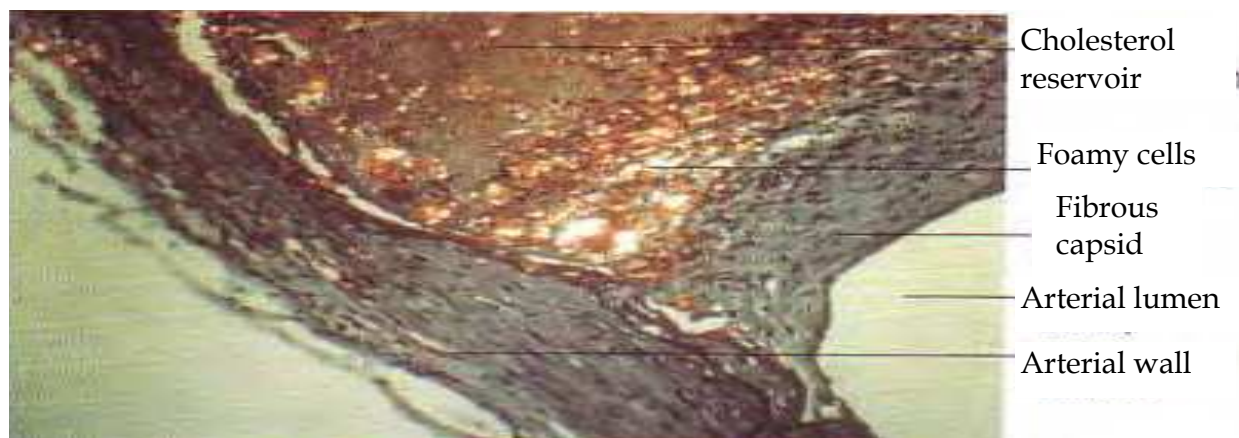

Fig. 3. The point of the atheromatous plaque, on which active enlargement occurs: formation of new foam cells and increased cholesterol uptake contribute to increased plaque instability (adopted from Durrington & Sinderman, 2002).
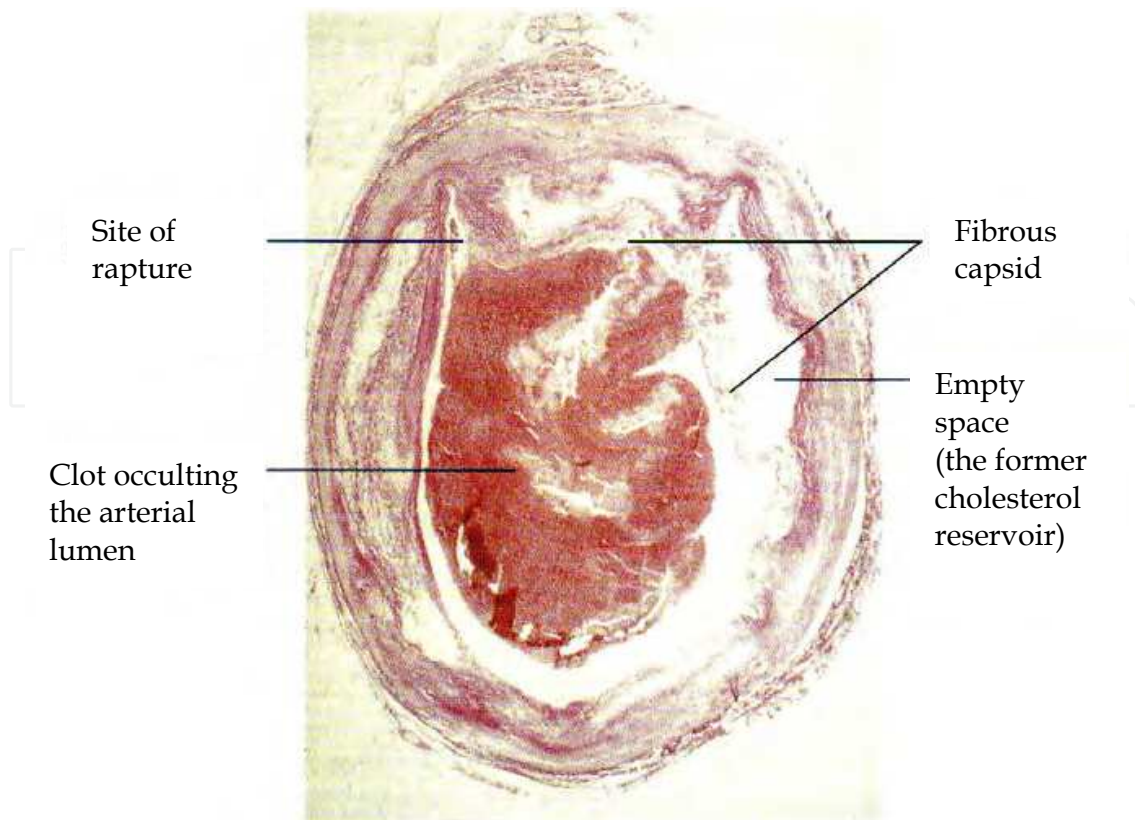
Fig. 4. A raptured ahteromatous plaque, in which the cholesterol reservoir has evacuated itself under the fibrous capsid. A clot in the endothelial surface at the site of rapture occults the lumen completely (adopted from Durrington & Sinderman, 2002).

1.2 Oxidized LDL

Oxidized LDL cholesterol in humans is found mainly in two types:

a.   conjugated form, attached to the atheromatous plaque and
b.   circulating form found in serum.

Oxidized LDL is produced following oxidation of LDL by free radicals and other oxidadive factors, a procedure called oxidative stress. The circulating oxLDL is the measurable fraction of oxLDL in plasma. Oxidized LDL is a key element of the pathway leading to the formation of the atheromatous plaque and has been extensively studied both as a marker of atheromatosis and as a possible target of therapeutic intervention. Circulating oxLDL is considered a risk marker for atherosclerosis (Toshima, 2000) and coronary heart disease (CHD) (Ehara et al., 2001; Holvoet et al., 2003; Toshima et al., 2000). Increased oxLDL levels in circulation and the vessel wall are associated with endothelial dysfunction (Penny et al., 2001) in such patients (Ehara et al., 2001; Holvoet et al., 1999; Nishi et al., 2002), contributing to atheromatous plaque instability (Ehara et al., 2001).

Oxidative modification of LDL leads to rapid focal accumulation in macrophages (Witztum & Steinberg, 1991), which is the first step of the atheromatous process. The increased retention time of LDL in the intima offers enhanced probability to be oxidized by free radicals produced by endothelium, smooth muscle cells or macrophages (Steinbrecher et al.,

1984). Oxidized LDL then acts chemotactic for monocytes and smooth muscle cells through binding to scavenger receptors (D. Li et al., 2002), leading to the formation of foamy cells. Oxidized LDL is also capable to elicit endothelial dysfunction by altering the secretory activity of endothelial cells (D. Li et al., 2002), inhibiting the nitric oxide-mediated vasodilatation through reduction of the expression of endothelial nitric-oxide synthase (eNOS), inducing the expression of adhesion molecules on the endothelium thus mediating the adhesion of monocytes to intima (D. Li et al., 2002), and inducing the expression of inflammatory cytokines (Steinberg, 1997). Indeed, oxLDL is a potent inducer of inflammation (Steinberg et al., 1989), contributing to the chronic inflammatory process which results to atherosclerosis (Ross, 1999).

1.3 Statins

The 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors, or statins, reduce serum TC, LDL cholesterol, apolipoprotein B (apoB), and, to a lesser degree, TG and Lp-a levels. Statins also have pleiotropic effects (Bellosta et al., 2000), such as the modulation of inflammatory molecules and monocyte maturation and differentiation (Bellosta et al., 2000), the suppression of smooth muscle-cells migration and proliferation (Bellosta et al., 2000), the reduction of the monocyte adhesion to the endothelium (Weber et al., 1997), the restoration of the impaired endothelium-dependent vessel wall relaxation (Jarvisalo et al., 1999), and the modification of cell-mediated LDL oxidation (Giroux et al., 1993; Aviram et al., 1998). All of the above mechanisms contribute to the reversion of atheromatosis. Undeniably, statins reduce the incidence of coronary events and are a cornerstone in the primary and secondary prevention of CHD (D.Y. Li et al., 2001). Previous studies have detected some efficacy in reducing the circulating oxLDL levels, but whether this effect is due to the reduction of LDL or is an independent, pleiotropic phenomenon remains a matter of controversy (Kwak & Mach, 2001; Robinson et al., 2005). Furthermore, little is known about the definite clinical benefit of such oxidative marker reduction.

The aim of the present study was to evaluate the efficacy of atorvastatin in reducing stenosis, to investigate the effect on oxLDL and to search for possible associations of oxLDL modification with changes of stenosis in patients managed conservatively and in pre-treated with percutaneous catheter interventional procedures patients with carotid atheromatosis. We hypothesise that atorvastatin therapy will confer remission of oxLDL levels in vivo and this will be associated with significant reduction of carotid artery stenosis.

2. Patients and methods

Between January 2005 and February 2008 a total of 100 patients were randomly selected from the lipid clinic and the carotid angioplasty clinic of a large tertiary hospital in Athens for inclusion in the study. Informed consent was obtained from each patient at recruitment according to our institutional policies. Eligible were patients with carotid artery atheromatosis from various causes (not only dyslipidemia) and with a range of predisposing factors. Exclusion criteria included: acute cardiovascular disease, severe or unstable angina pectoris, clinically evident cardiac failure, severe arrhythmias, recent surgical procedures, inflammatory diseases, active liver disease or liver impairment, excessive alcohol consumption (>4 drinks / day) or history of alcohol abuse, known allergic reaction to statins, poorly controlled diabetes mellitus as defined by a haemoglobin A1c (HbA1c) level of >7 %,

uncontrolled hypertension indicated by systolic blood pressure (SBP) >140 mmHg and/or diastolic pressure >85 mmHg, history of deep vein thrombosis, bleeding tendency, serum triglycerides >350 mg/dl, evidence of thyroid dysfunction, use of systemic steroids or other anabolics, pernicious anaemia, impaired vitamin B12 or folate acid levels, abnormal serum urate at baseline, serum creatinine phosphokinase elevation of >1.5 fold at baseline, pregnancy or lactation, and end-stage renal disease or dialysis.

Patients were allocated into two groups according to the degree of carotid artery stenosis: those with arterial lumen occlusion of ≥70% in at least one common or internal carotid vessel consisted group A; those with stenosis <70% comprised group B. Patients in both groups were naive to statin therapy or if otherwise, a 6-month washout period was allowed before enrolment in the study. Group A underwent percutaneous transluminal carotid angioplasty with stenting by the same interventional cardiologist, prior to the initiation of statin therapy. Those patients were additionally administered clopidrogrel and salicylate. Both groups had to follow an American Heart Association step II diet and were encouraged to exercise.

According to the study protocol, all patients were placed on atorvastatin once daily at bedtime in individualised doses, tittered to achieve and maintain serum LDL cholesterol levels of <100 mg/dl (and ideally <70 mg/dl, if hypertension, renal impairment, smoking, hyperlipidemia, symptomatic peripheral arterial obstructive disease, or diabetes mellitus were present). Patients were prescribed statins even in the absence of hyperlipidemia, as the aim of the study was to investigate the effect of statin on oxLDL and carotid stenosis in a common atherogenic patient population. The most common doses used to achieve the above levels of LDL ranged between 10 to 40 mg, while seldom it was required to administer higher doses such as 60 mg (median atorvastatin dose for the total population = 20 mg, range 10 – 60 mg). The use of other drugs known to act synergistically with statins causing rhabdomyolysis was prohibited during the study. Adverse events were assessed in every visit in a non-specific manner: every newly reported symptom was documented as possible adverse reaction due to statin therapy and subsequently evaluated by an expert in clinical biochemistry. Adherence to the medication regimen was assessed indirectly by the low LDL levels compared with baseline.

Medical anamnesis, anthropometrics, smoking habits, blood pressure, and laboratory investigations comprising of complete blood count, fasting glucose, HbA1c, liver and kidney biochemistry, detailed lipid profile (TC, LDL cholesterol, HDL cholesterol, serum TG, apoB, and apolipoprotein A), urate, B12 and folate, thyroid function tests, homocysteine, Lp-a, and oxLDL were obtained at baseline and during follow-up visits, which were arranged at baseline, one, three, and six months; the final assessment was carried out in 12 months. Blood samples were collected after an at least 12-hour fast and a light, low-fat meal the night before sample collection was advised. Venous blood samples were collected in standard biochemistry vacutainer tubes. For the analysis of homocysteine and whole blood count, ethylenediaminetetraacetic acid (EDTA) vacutainer was used. Serum for biochemistry analysis was obtained by centrifugation (4000 g) at 4°C for 7 min and was immediately tested.

Lipid profiles (TC, HDL, TG) were determined using commercially available enzymatic colourimetric methods (Dade Behring, Newark, USA) with a Dade Behring analyser. LDL was calculated with the use of Friedewald's formula as all had TG <350 mg/dl (Puccetti et

al., 2002). For the measurement of circulating oxLDL, a commercially available kit (Mercodia, Uppsala, Sweden), based on a double antibody (4E6 and mouse monoclonal antiapoB) (Holvoet et al., 1996) capture ELISA test, was used. This method primarily detects malondialdehyde LDL (MDA-LDL). The normative range (reference range) in our lab was 31-61 mU/l. Apolipoprotein A, B and Lp-a were measured using immuno-nephelometry with rabbit antisera (Dade Behring, Newark, USA) in a Dade Behring analyser.

The evaluation of stenosis was conducted by Triplex ultrasonography using an Apogee 800 plus scanner with a 7.5 MHz transducer (ATL Inc., Bothell WA, USA) at baseline and 12 months. The stenosis was calculated in three sections in each common and internal carotid artery, and the final measure was the mean value of the three. The value of stenosis in the most occluded vessel was used in the statistical analysis. Specifically, the internal carotid artery (ICA) and common carotid artery (CCA) bilaterally were evaluated for each patient using coloured and grey Doppler ultrasonography. An effort was made to completely visualize the vessels. Additionally, the pulse wave was estimated with Doppler phasmatometry as well as the blood flow velocity of the two vessels. Results were recorded in a validated form. Stenosis was defined as the presence of visual plaque in coloured or grey Doppler. The degree of stenosis was calculated by measuring the decrease of the lumen diameter and the maximum systolic blood flow velocity. In difficult cases, other parameters were taken into account, such as ICA/CCA max blood flow velocity ratio and the ICA end-diastolic velocity. A degree of stenosis >70% was considered as sever and angioplasty was advised. A degree of stenosis between 60 – 70% was defined as high, between 50 – 60% as moderate and <50% as mild. High, moderate and mild stenoses were treated conservatively. The intima media thickness (IMT) and plaque morphology were not studied due to specific lab requirements, not readily available in our institution.

2.1 Statistical analysis

Continuous variables were presented as mean values ± standard deviation, while qualitative variables were presented as absolute and relative frequencies. Normality tests were applied using the Kolmogorov-Smirnov criterion as well as Shapiro-Wilk test. Univariate analysis was initially applied to test the associations of oxLDL with carotid stenosis for each patient group as well as to identify first order correlations with various clinical parameters. Correlations between skewed continuous or discrete variables were evaluated using Spearman's p-coefficient, whereas correlations of normally distributed variables were evaluated by calculating the Pearson's r-coefficient. Comparisons between normally distributed, continuous variables and categorical variables were made using the Student t-test. Analysis of categorical data was carried out with the [chi]2 test or Fischer's exact test when appropriate.

The association of oxLDL with carotid stenosis was also tested through multiple Cox proportional hazard model. The results obtained were presented as Hazard Ratios (HR) and the 95% Confidence Intervals (CI). A backward elimination procedure was applied to all multivariate models (using P<5% as the threshold for removing a variable from the models). All models were adjusted for age, gender, SBP and TC. Kaplan-Meier curves concerning stenosis over the study period were plotted and Log rank test was performed. All reported P-values were based on two-sided tests and compared to a significance level of 5%. STATA 8.0 software (Stata Corporation, 2003, Texas, USA) was used for the analysis.

3. Results

3.1 Patients' characteristics

A total of 612 patients were evaluated, of which 123 fulfilled the eligibility criteria; finally, 100 had complete data to enter the analysis, 76 males and 24 females, median age 68 years (range 45-81). Diabetes mellitus was recorded in 26 of the 100 patients and hypertension in 66. Twenty patients had metabolic syndrome according to the national cholesterol education programme-adult treatment panel III (NCEP-ATP III) criteria (National Cholesterol Education Program (NCEP), 2001). Active smoking (defined as current of discontinued as far back as 5 years) was reported by 58 patients. Mean atorvastatin dose at baseline was 24.31±11.49 mg for group A and 20.62±10.39 mg for group B (p=0.1). By the end of the study period, the respective mean values were significantly increased to 30.45±16.27 mg for group A (p=0.044) and 28.75±17.57 mg for group B (p=0.007).

Each of the study group (A and B) comprised 50 patients. The two groups were comparable with regard of their baseline characteristics (table 1).

3.2 Lipid profile and oxidzed LDL

Mean serum TC, LDL-cholesterol, TG, Lp-a, homocysteine, and oxLDL were significantly reduced at 12 months compared to baseline (table 2). Specifically, mean oxLDL dropped from 62.26±22.03 to 44.49±21.75 mU/l (p<0.001). A marked decrease was noticed during the first 6 months and a plateau thereafter (figure 5).

Characteristic	Total	Group A	Group B	P value
Males / females	72 / 28	36 / 14	36 / 14	
Mean age in years ± SD	67.57±7.15	68.46±5.71	66.68±8.31	0.21
Number of pts with DM (percentage)	37 (37%)	18 (36%)	19 (38%)	0.83
Number of pts with HTN (percentage)	67 (67%)	36 (72%)	31 (62%)	0.29
Number of smokers (percentage)	54 (54%)	29 (54%)	25 (46%)	0.33
Number of pts with CAD (percentage)	51 (51%)	24 (47%)	27 (53%)	0.55
Mean ± SD TC (mg/dl)	232.23±47.8	235.24±49.2	229.22±46.7	0.53
Mean ± SD LDL cholesterol (mg/dl)	151.27±41.7	154.16±42.8	148.84±40.9	0.52
Mean ± SD HDL cholesterol (mg/dl)	51.97±12.7	52.12±12.1	51.82±13.4	0.9
Mean ± SD TG (mg/dl)	145.59±73.1	146.04±73.2	145.14±73.7	0.95
Mean ± SD oxLDL (mU/l)	64.66±24.8	65.8±25.3	63.53±24.5	0.65
Mean ± SD homocysteine (mU/l)	13.99±4.8	13.5±4.6	14.47±5.1	0.32

Pts: patients, DM: diabetes mellitus, HTN: arterial hypertension, MS: metabolic syndrome, SD: standard deviation, LDL: low density lipoprotein, HDL: high density lipoprotein, CAD: coronary artery disease, TC: total cholesterol, TG: triglycerides, oxLDL: oxidized LDL
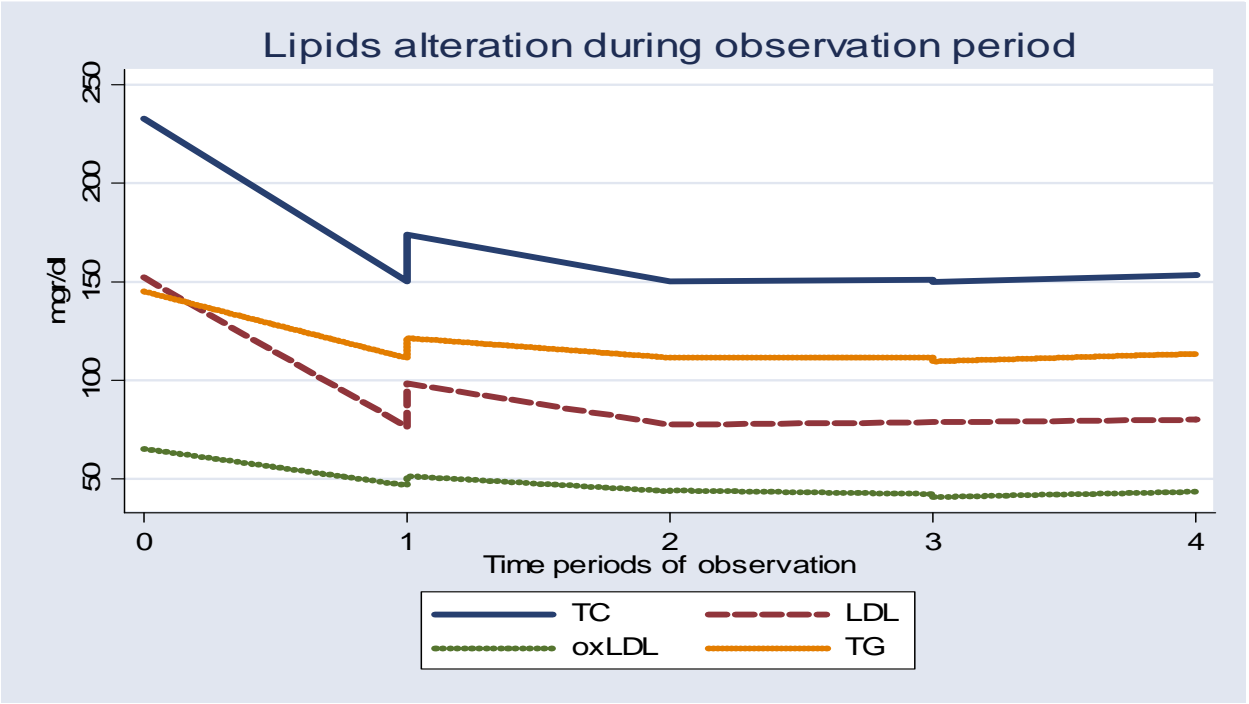
Table 1. Study population baseline characteristics.

A significant correlation between LDL and oxLDL levels was detected (Pearson's correlation coefficient r=0.7, p<0.01) (figure 6). Similar correlation was found between oxLDL and apoB levels (r=0.65, p<0.001), while no significant correlation was shown with Lp-a.

Between smokers mean oxLDL was reduced from 60.68±24.09 at baseline to 45.84±24.89 mU/l at the end of study period (difference 14.84 mU/l, p = 0.0036). Similarly, between non-smokers it was reduced from 69.33±25.11 to 40.36±5.6 mU/l (difference 28.97 mU/l, p<0.001). Non-smokers had approximately double decline of oxLDL levels compared to smokers. Carotid artery stenosis was reduced between smokers from 29.68±25.59% at baseline to 23.06±21.71% at 12 months (p = 0.002). Non-smokers also presented significant reduction of stenosis during the study period (24.67 ± 26.22% vs 20 ± 21.45%, p = 0.004). Non-smokers and smokers had similar decline of carotid stenosis in 12 months (6.61% vs 4.67%, table 3).

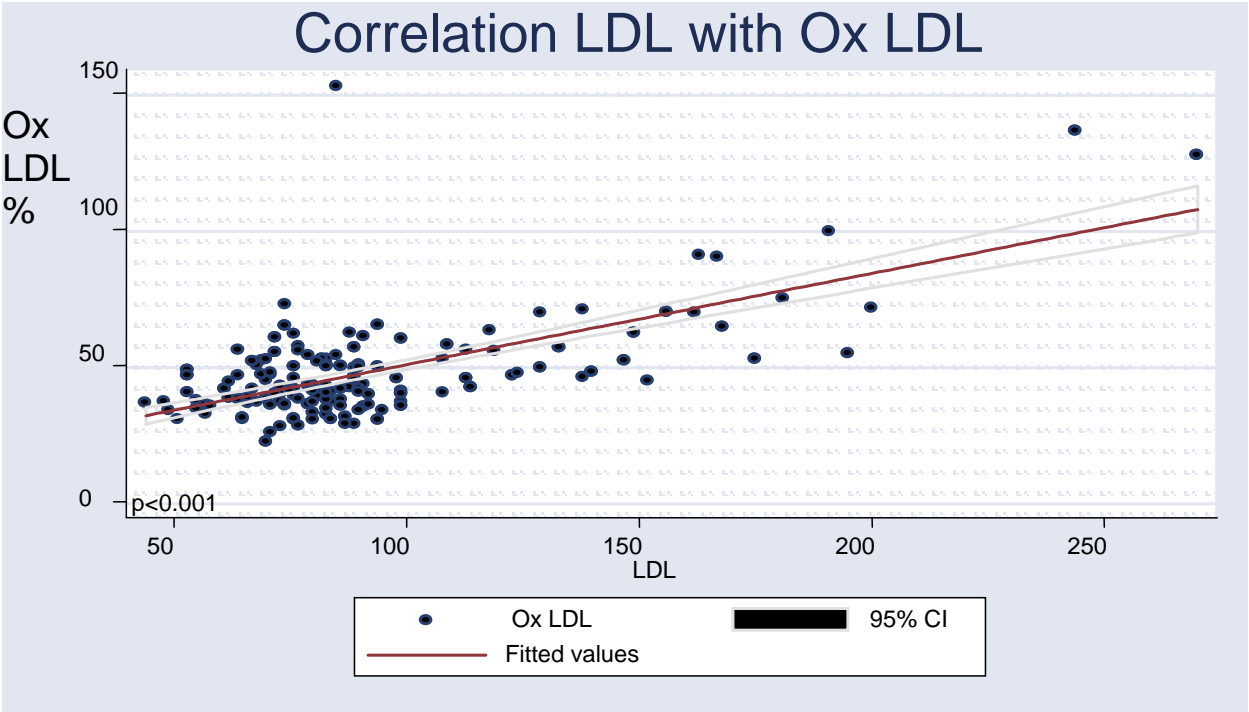| Investigations	Total	Group A	Group B
TC (mg/dl) baseline TC (mg/dl) 12 months p value	232.23 ± 47.8 153.36±17.2 <0.0001	235.24±49.1 154.24±16.9 <0.0001	229.22±46.7 152.48±17.7 <0.0001
LDL cholesterol (mg/dl) baseline LDL cholesterol (mg/dl) 12 months p value	151.5±41.7 79.75±12.7 <0.0001	154.16±42.8 79.54±13.2 <0.0001	148.84±40.9 79.96±12.3 <0.0001
TG (mg/dl) baseline TG (mg/dl) 12 months p value	145.59 ± 73.1 111±53.1 0.0002	146.04±73.2 112.1±54.7 0.01	145.14±73.7 109.9±51.96 0.0069
OxLDL (mU/l) baseline OxLDL (mU/l) 12 months p value	64.67±24.8 43.38±18.9 <0.0001	65.8±25.3 42.16±17.6 <0.0001	63.53±24.6 44.65±26.1 0.0007
HDL cholesterol (mg/dl) baseline HDL cholesterol (mg/dl) 12 months p value	51.97±12.7 51.32±15.5 0.74	52.12±12.1 52.22±16.3 0.97	51.82±13.4 50.42±14.8 0.62
Homocysteine (mg/dl) baseline Homocysteine (mg/dl) 12 months p value	13.99±4.8 11.89±3.5 0.0006	13.5±4.6 11.88±3.8 0.057	14.48±5.1 11.9±3.4 0.0036
Apolipoprotein A (mg/dl) baseline Apolipoprotein A (mg/dl) 12 months p value	156.57±26.7 160.35±25.3 0.3	156.46±27.3 162.02±23.7 0.28	156.68±26.4 158.68±27.1 0.7
Apolipoprotein B (mg/dl) baseline Apolipoprotein B (mg/dl) 12 months p value	129.95±31.3 77.1±11.8 <0.0001	131.84±31.4 77.58±13.1 <0.0001	128.05±31.4 76.62±10.47 <0.0001
Lp-a (mg/dl) baseline Lp-a (mg/dl) 12 months p value	25.08±23.8 27.72±29.1 0.48	25.67±24.1 29.42±29.8 0.49	24.47±23.8 26.01±28.7 0.77

LDL: low density lipoprotein, HDL: high density lipoprotein, TC: total cholesterol, TG:triglycerides, oxLDL: oxidized LDL, Lp-a: lipoprotein a

Table 2. Comparison of mean ± standard deviation and respective P-values of measured laboratory investigations at baseline and 12 months, in the total population, and the two groups.

TC: total cholesterol, LDL: low density lipoprotein cholesterol, oxLDL: oxidized LDL, TG: triglycerides, 0=baseline, 1=one month, 2=three months, 3=six months, 4=twelve months.

Fig. 5. Time curve of change of total cholesterol, LDL cholesterol, triglycerides and oxidized LDL levels during the observation period.

LDL: low density lipoprotein cholesterol, oxLDL: oxidized LDL, CI: confidence intervals.

Fig. 6. Correlation of low density lipoprotein with oxidized LDL levels at baseline (Pearson's correlation coefficient r=0.7, p<0.001).

In further analysis, the group of smokers was subdivided to mild (≤5 cigarettes/day), moderate (5 – 15 cigarettes/day) and heavy (≥15 cigarettes/day) smokers. The statistical significant reduction of oxLDL levels and degree of carotid stenosis was apparent in the subgroup of mild smokers (oxLDL at baseline 48.24±8.74 mU/l vs 41.54±9 mU/l at 12 months, p = 0.027 and stenosis at baseline 27.63±25.68% vs 23.42±21.74% at 12 months, p = 0.009), while it was not apparent in the subgroups of moderate and heavy smokers (oxLDL at baseline 86.82±37.7 mU/l vs 42.92±10.77 mU/l at 12 months, p = 0.077 and stenosis at baseline 34±31.9% vs 22±24.9% at 12 months, p = 0.186, for moderate smokers; respective values for oxLDL were 66.29±15.88 mU/l vs 34.81±5.48 mU/l, p = 0.06 and for stenosis 32.14±24.13% vs 22.86±22.8%, p = 0.174, for heavy smokers). The above described effect of smoking was taken into consideration during Cox-regression analysis.

	Smokers	P value	Non Smokers	P value
OxLDL (mU/l) baseline 12 months difference	60.68±24.09 45.48±24.89 14.84	0.0036	69.33±25.11 40.36±5.6 28.97	0.001
Stenosis (%) baseline 12 months difference	29.68±25.59 23.06±21.71 6.61	0.002	24.67±26.22 20±21.45 4.67	0.004
Correlation of oxLDL change with stenosis change in 12 months	Pearson's r = 0.412	0.021	Pearson's r = 0.198	0.03

oxLDL: oxidized LDL.

Table 3. Comparison of mean oxidized LDL values and degree of carotid stenosis change during the 1 year follow-up period, between smokers and non-smokers.

Within group B, the subgroup of patients with high degree of stenosis (>60%) had oxLDL 63.47±19.18 mU/l at baseline, while those with moderate and mild degree of stenosis (<60%) had 40.32±20.72 mU/l (p<0.001). Corresponding values at 12-months were 33.18±17.78 mU/l and 38.81±29.02 mU/l, representing a marked decline for patients with >60% initial stenosis and a far less decline for patients with <60% initial stenosis; yet those differences were not statistically significant (table 4).

	Stenosis >60<70%	Stenosis <60%	P value
Baseline Mean oxLDL	63.47±19.18 mU/l	40.32±20.72 mU/l	< 0.001
12 months Mean oxLDL	33.18±17.78 mU/l	38.81±29.02 mU/l	NS

LDL: low density lipoprotein cholesterol, oxLDL: oxidized LDL, NS: non significant.

Table 4. Comparison of mean oxidized LDL levels at baseline and 12 months within patients of group B (n = 50), according to degree of stenosis at enrollment.

3.3 Anthropometrics

Body mass index (BMI), weight, waist circumference and waist:hip ratio did not change significantly during the study period.

3.4 Carotid stenosis

Patients in group A had null stenosis at recruitment due to prior angioplasty with stenting. At the end of the 12-month statin therapy, no case of clinically important restenosis (>70%) was reported in this group (as restenosis was defined any increase of the carotid lumen diameter >5%). Patients in group B had mean percentage of stenosis at baseline 47.6±13.2%, which was significantly reduced following 12-month statin therapy (37.7±15.7%, p<0.001) (table 5).

	Baseline	12 months	P value
Mean (%) carotid stenosis ± standard deviation	47.6 ± 13.2	37.7 ± 15.7	0.001

Table 5. Change of the percentage of carotid artery stenosis between baseline and 12months for patients in group B.

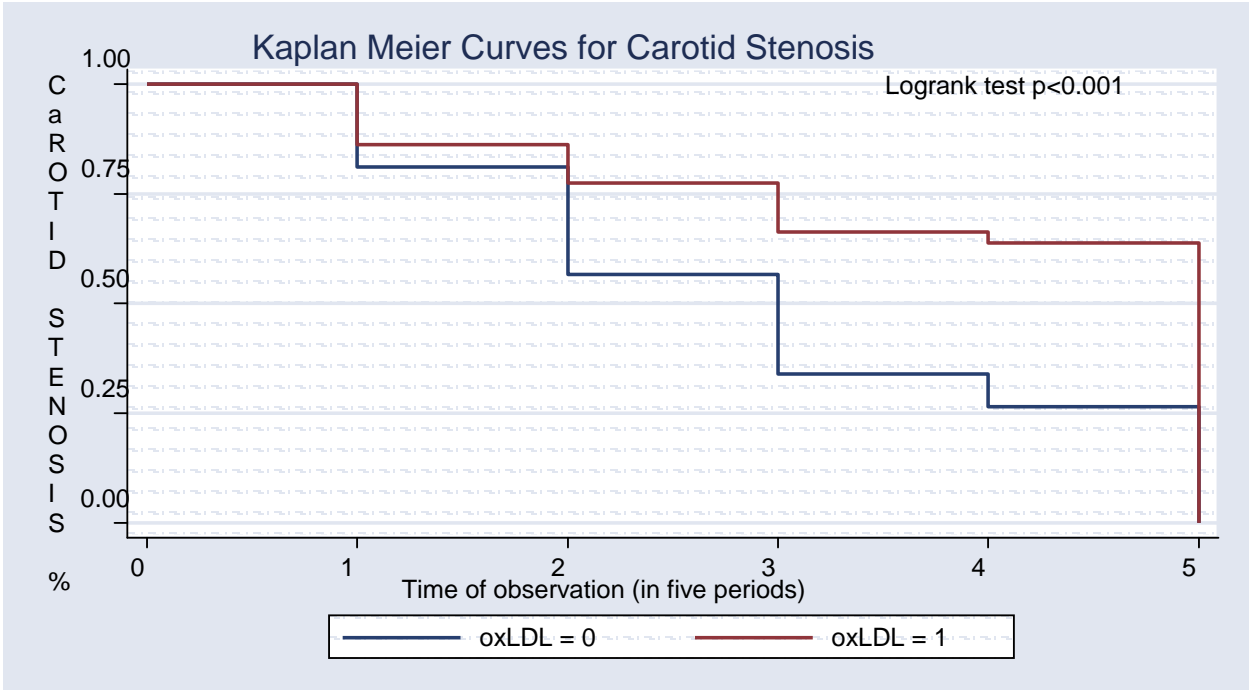### 3.5 Association of stenosis with oxidized LDL

Group B patients in the highest quartile of oxLDL values had a 12-month risk ratio for restenosis of 1.025, 95%CI=1.006-1.044, p=0.0083 (figure 7). After adjusting for gender, age, smoking, SBP, TC, and LDL levels, these patients demonstrated a HR for restenosis of 4.319 compared with those in the lowest quartile (p<0.001, figure 7). This means that an increase of oxLDL by one unit increases the degree of carotid stenosis by 2.5%, for patients in group B. A weak but significant correlation was detected between oxLDL levels and the degree of carotid artery stenosis (r=0.17, p=0.018). Similar correlation was found between LDL cholesterol levels and carotid stenosis (r=0.18, p=0.0085). The strength of Pearson's correlation of mean oxLDL change with degree of carotid stenosis change during the 12-month period was greater for smokers compared to non-smokers (table 3).

3.6 The effect of LDL levels

Patients in group B who achieved LDL levels <70 mg/dl during the observation period had a greater (28.08±28% vs 22.31±22.7%, difference 5.77%, p = 0.06) reduction of carotid stenosis compared to those with LDL levels between 70 and 100 mg/dl (26.98±25.3% vs 21.35±21.3%, difference 5.63%, p < 0.001), but this difference was not statistically significant. Thus, in conservatively treated group B, further reduction of LDL than the limit of 100 mg/dl was not associated with additional improvement of stenosis.

4. Discussion

This study demonstrates that atorvastatin administered in indivudualised doses, tittered to maintain serum LDL cholesterol levels <100 mg/dl, significantly decreased lipid profile and oxLDL, reduced carotid artery stenosis in patients managed conservatively and prevented restenosis in patients with prior angioplasty. Oxidized LDL in this study correlated positively with the degree of carotid artery stenosis; it was also shown by multivariate analysis that oxLDL represented an independent risk factor for restenosis. To our knowledge this is the first prospective study with a long observation period of 12 months to report such a clear, significant reduction of oxLDL levels following atorvastatin therapy for carotid atheromatosis of various causes and to report an association of the degree of oxLDL reduction with remission of carotid stenosis. It is also of major importance that this robust, long-standing decline of oxLDL was achieved with doses of atorvastatin used in everyday clinical practice. Interestingly, this beneficial effect was completed in the first six months, while practically no further reduction was noticed past this time point.

oxLDL=0: low quartile of oxLDL levels, oxLDL=1: high quartile of oxLDL levels, 0=baseline, 1=one month, 2=three months, 3=six months, 4=twelve months.

Fig. 7. Kaplan Meier survival analysis for the estimation of the risk ratio for restenosis according to the levels of oxidized LDL (oxLDL). With red line those with oxLDL levels in the highest quartile of the values. With blue line those with oxLDL levels in the lowest quartile of the measurements (risk ratio 1.025, logrank test p<0.001).

The mechanism by which statins modulate oxLDL levels has been controversial in the literature. Moreover, the association of oxLDL level modification with improvement of carotid atheromatosis and clinical outcome is not unequivocally established by large, double-blinded, randomised trials. Under this perspective, the present observational study provides reasonable evidence that reducing oxLDL may independently improve carotid stenosis.

Carotid IMT is a validated measure of carotid atherosclerosis. It is well established that carotid atherosclerosis, serves as an independent surrogate marker for CHD (Vasankari et al., 2001) and CVD (van Tits et al., 2006). Nevertheless, in the present study it was preferred to estimate the degree of carotid stenosis with a more direct approach, because this is more readily available in most hospital settings and because there is an obvious relation with clinical symptoms and signs. Besides, it represents a reliable method with sufficient reproducibility and it is practically the method of choice when evaluated patients candidate for endarterectomy or angioplasty. Evaluating carotid stenosis in turn, is an established method for estimating coronary risk (Vasankari et al., 2001) and cardiovascular risk (van Tits et al., 2006). Other parameters of vessel wall function, such as IMT and plaque morphology, even if clearly associated with cardiovascular risk in the literature, require well equipped laboratory and are not readily available in our hospital. Future research on the field should, ideally, comprise such measurements.

Oxidized LDL has long been recognized as a risk factor for carotid atherosclerosis in asymptomatic men (Liu et al., 2004) and has also been linked with CVD (Robbesyn et al., 2004). Oxidized LDL levels (Papathanasiou et al., 2008), autoantibodies against epitopes of oxLDL (Papathanasiou et al., 2008) and oxLDL:LDL ratio (Vasankari et al., 2001) are independently associated with increased risk for coronary atheromatosis and ischemic heart disease. Increased levels of oxLDL (Ehara et al., 2001) and MDA-LDL (Holvoet et al., 1999) in such cases are related to plaque instability. On the other hand, it has been reported that oxLDL is weakly associated with carotid IMT, but not with carotid plaque occurrence (Hulthe & Fagerberg, 2002). Oxidized LDL impairs endothelium relaxation (Harrison et al., 1987) by inhibition of the expression of eNOS and of the transport pathways of nitric oxide (NO) from the endothelial cell, reduces the responsiveness of smooth muscle cell to NO (Keaney et al., 1996), inhibits the NO-mediated vasodilation (Harrison et al., 1987; Simon et al., 1990; Steinberg, 1997), induces the expression of adhesion molecules (Frostegard et al., 1990), acts directly chemotactic to circulating monocytes (Steinberg, 1997), stimulates endothelial cells to produce MCP-1 (Cushing et al., 1990), facilitates monocyte adhesion to intima (Mehta et al., 1995), exhibits cytotoxic properties against endothelial cells (Steinberg, 1997), and induces the expression of inflammatory molecules (Steinberg, 1997). All of the above contribute directly to dysfunction of the endothelium (Witztum & Steinberg, 1991) and foam cell formation, which is the first step in the development of fatty streaks (Ross, 1999), the first visible step of atherosclerosis. These effects are mediated by preferential binding of oxLDL with type A scavenger receptors (SRA, SRA-II and CD36) on subendothelial resident macrophages and smooth muscle cells (Li et al., 1995) and lectin-like oxLDL receptor-1 (LOX-1) on endothelial cells (Sawamura et al., 1997) rather than the typical LDL receptor, resulting in an unrestricted uptake of cholesterol.

Statins reduce the incidence of cardiovascular events, an effect attributable to their hypocholesterolemic properties (Archbold & Timmis, 1999). However, the extent of clinical benefit and accumulating laboratory evidence suggest additional mechanisms of action, the so-called pleiotropic effects (Bellosta et al., 2000). The most important among such effects are the suppression of smooth muscle cell migration and proliferation (Bellosta et al., 1998), the reduction of monocyte adhesion to the vascular endothelium (Weber et al., 1997), the improvement of endothelial function (Jarvisalo et al., 1999), the inhibition of cell-mediated LDL oxidation (Aviram et al., 1998; Giroux et al., 1993), the immuno-modulation of

monocyte maturation and differentiation, and the modification of production of inflammatory cytokines (Rothe et al., 1999).

Atorvastatin suppresses cellular uptake of oxLDL from differentiating monocytes by reducing the expression of LOX-1 and scavenger receptors (Fuhrman et al., 2002) and accelerates the LDL-receptor-mediated removal of the non oxidized LDL particles (Vasankari et al., 2005). Hydroxymetabolites of atorvastatin protect the LDL against oxidation (van Tits et al., 2006). The antioxidant potency of atorvastatin metabolites has been confirmed by the reduction of IgG antibodies against LDL, a marker well-associated with CHD (Aviram et al., 1998). It has even been reported that these active atorvastatin metabolites may have greater anti-atherosclerotic effects than other statin molecules (Mason et al., 2004).

In acute coronary syndromes, atorvastatin therapy was linked to modulation of short- and long-term immune response towards LDL due to inhibition of lipoprotein-associated phospholipase A2 (Lp-LPA2) enzyme (Papathanasiou et al., 2008). The apparent benefit from statin therapy after acute coronary events may also be attributed to the stabilization of the plaque and removal of oxLDL from the vessel wall (Tsimikas et al., 2004). Increased mobilization of oxidized phospholipids from the vessel wall, transient binding with apoB-100 particles and clearance from the circulation may be the possible underlying mechanism. Under this perspective the increase in oxLDL:apoB ratio detected with atorvastatin therapy might represent a marker of oxLDL efflux from the vessel wall. Removal of oxLDL contributes to improved endothelial function as oxLDL is highly immunogenic and vasoconstrictive. In our study there was no significant change in oxLDL:apoB ratio. Atorvastatin also inhibits the oxLDL-mediated LOX-1 expression by endothelial cells, the uptake of oxLDL in endothelium and the oxLDL-mediated reduction of protein kinase B (PKB) phosphorylation (Li et al., 2001). The activation of PKB is critical for the expression of eNOS, which promotes vessel relaxation. However, a meta-analysis provided no clear evidence that statin therapy have a favourable effect on oxLDL (Balk et al., 2003).

In STAT trial (Mulder et al., 2007) the antibodies against oxLDL were equally decreased with both aggressive and conventional lipid-lowering therapy. This indicates that the statin-related reduction of oxLDL is not a dose-dependent phenomenon, a finding which is in agreement with our results. It might therefore represent a pleiotropic effect, independent -at least partially- from the hypo-cholesterolemic action. A study by Orem et al. (2002) detected a significant decrease of autoantibodies against oxLDL with low doses of atorvastatin (10 mg), similar to doses used in our study. In statin exposed patients, intensification of the regimen offers no additional benefit and only those with LDL >125 mg/dl benefited from a more aggressive statin therapy (Mulder et al., 2007). Statins have a dose-related response with regard to clinical outcome, but this dose-related response has not been confirmed with regard to oxidative stress (Ky et al., 2008). This might alternatively be explained by the hypothesis that statins achieve their uttermost benefit on oxLDL within a certain time point (Mulder et al., 2007), after which further continuation of treatment serves only the purpose of maintenance. Atorvastatin has been shown to reduce small dense LDL subfractions, remnant-like particles cholesterol and oxLDL, and improve endothelial function, after just few weeks of therapy (Miyagishima et al., 2007; Sakabe et al., 2003). Such time-related effect has not been fully elucidated, but may possibly account for our finding that in the first six months there was an accelerated decline of oxLDL levels followed by a milder reduction rate thereafter.

Additional pleiotropic effects of statins have been reported in the literature and might account for the observed beneficial effects in the current study. Lysophosphatidylcholine is elevated during LDL oxidation and is responsible for some of the biological effects of oxLDL. Atorvastatin alters the ability of oxLDL to impair the endothelium relaxation, by modulating the hydrolysis of phosphatidylcholine to lysophosphatidylcholine when LDL is being oxidized (Zhu et al., 2000). Statins remove predominately "aged LDL" from plasma, which is more prone to oxidation (Orem et al., 2002), through stimulation of hepatic LDL receptor activity and inhibition of very-low density lipoprotein (VLDL) and LDL production by the liver cells (Orem et al., 2002). Statins also reduce oxygen species generation (Ky et al., 2008). Atorvastatin promotes adipocyte uptake of oxLDL in rabbits by increasing the expression of CD36 and peroxisome proliferators-activated receptor γ (PPARγ) in adipocytes (Zhao & Zhang, 2004). The increased expression of such receptors by adipocytes results to internalization of oxLDL and clearance from plasma, converting adipocytes to an oxLDL-buffering pool (Zhao & Zhang, 2004). Reduction of oxLDL in patients with CHD with atorvastatin 10 mg parallel with an increase of adiponectin, which has anti-atherogenic, anti-inflammatory and anti-diabetic properties through reduction of insulin resistance (Miyagishima et al., 2007). The CARDS study reported a significant degree of preventive activity of atorvastatin against myocardial infarction in eucholesterolemic diabetic patients, conceivably attributed to such improvement of insulin sensitivity (Miyagishima et al., 2007). Statins also diminish the expression of CD40 and CD40 ligand in vascular cells, smooth muscle cells and macrophages, which are promoted by oxLDL and are considered proatherogenic (Schonbeck et al., 2002). Other anti-inflammatory pathways include reduction of C-reactive protein (Hogue et al., 2008), chemokines, major histocompatibility complex II molecules, matrix-degrading enzymes, and procoagulant tissue factor (Schonbeck et al., 2002). Atorvastatin reverses the oxLDL-mediated inhibition of vascular endothelial growth factor-induced endothelial progenitor cell differentiation via the phosphatidylinositol 3 kinase/Akt pathway (Imanishi et al., 2003), which restores the oxLDL-related inhibition of mature endothelial cells migration (Imanishi et al., 2003). This could improve neovascularization and collateral vessel formation in response to tissue ischemia. Atorvastatin also suppresses platelet activity (Puccetti et al., 2005) by reducing the expression of CD36 and LOX-1, which are present in platelets (Puccetti et al., 2005; Sawamura et al., 1997), thus inhibiting the oxLDL-mediated platelet hyperactivity (Puccetti et al., 2005). Statins reduce the oxLDL-derived expression of adhesion molecules (E- and P-selectins, vascular cell adhesion molecule 1 [VCAM-1] and intercellular adhesion molecule 1 [ICAM-1]) in human coronary artery endothelial cells, through up-regulation of eNOS expression, which regulates the expression of adhesion molecules in endothelial cells (Li et al., 2002). Statins also diminish the oxLDL-mediated activation of nuclear factor-κB (NF-κB) (D. Li et al., 2002), which regulates the transcription of adhesion molecule genes (Robbesyn et al., 2004). In diabetic patients with dyslipidemia atorvastatin reduced CVD and markers of inflammation, adhesion and oxidation, such as C-reactive protein (CRP), soluble ICAM-1, soluble VCAM-1, E-selectin, matrix metalloproteinase 9, secretory phospholipase A2 (sPLA2), and oxLDL, the latter by 38,4% (Hogue et al., 2008). Moreover, the change of oxLDL levels correlated with the change of sICAM-1 and E-selectin levels, suggesting that statins could possibly counteract the oxLDL-associated increase of NF-κB, and therefore, the production of such cell adhesion molecules (Hogue et al., 2008). Statins also enhance

scavenger receptor expression in macrophages, and increase plaque stability via reduction of metalloproteinases (Hogue et al., 2008).

The reduction of oxLDL and of carotid stenosis in our study was relevant for both smokers and non-smokers. However, subsequent subgroup analysis showed that the beneficial effect of statin use concerns mostly the subgroup of mild smokers, while no such effect was noticed for moderate and heavy smokers. How smoking may diminish the beneficial effect of statins on oxLDL and carotid stenosis is not yet clarified in the literature. A reasonable assumption might be that, since smoking increases the oxidative stress, it contributes to enhanced LDL oxidation (Van Himbergen et al., 2004). Moreover, studies in animal models, have demonstrated that smoking alters the immunologic response to oxLDL by reducing the production of antibodies against these molecules, i.e. causing a kind of immune suppression regarding the response to oxLDL. Thus, it has been shown to increase carotid IMT (Tani et al., 2004).

The Mercodia oxLDL detects the MDA-modified apoB (Holvoet et al., 1996). It has been proposed that oxLDL looses its predictive value for CVD when adjustment for apoB level is performed (Ky et al., 2008). In several studies though, a significant reduction of Mercodia oxLDL with atorvastatin 10 mg was still detected even after adjustment for apoB, (Holvoet et al., 2003; Ky et al., 2008; van Tits et al., 2006), while in other studies no adjustment for LDL or apoB levels was made (Ky et al., 2008; Sasaki et al., 2002). In our study the oxLDL:apoB ratio remained unchanged, but in the multivariate analysis the reduction of oxLDL was still significant after adjustment for apoB and LDL levels.

In patients with familial hypercholesterolemia a lack of association between oxLDL and IMT was reported at baseline, however two years therapy with atorvastatin 80 mg was associated with regression of carotid IMT (van Tits et al., 2004). The LDL subfraction profile and autoantibodies against oxLDL remained unchanged. Nevertheless, the rate of oxidation and the amount of dienes formed decreased and this was linked to lessening of atherosclerosis. In our study the reduction of carotid stenosis was associated with decreased oxLDL levels. Besides, the unchanged oxLDL autoantibodies levels do not preclude the reduction of oxLDL, as was indicated in another study involving dialysis patients, where atorvastatin therapy reduced plasma oxLDL, whereas oxLDL autoantibodies did not changed significantly (van den Akker et al., 2003).

Disadvantages of the study were the relatively small size, the lack of a control group comprising of patients with carotid stenosis not on statin therapy, which would be unethical, the fact that researchers were not blinded to the patients' status, the lack of randomization of the dose-schedules and the use of only one method to detect oxLDL.

5. Conclusion

This prospective, cross-sectional study with such a long observation period provided enough evidence to postulate a favourable effect of low-dose atorvastatin therapy on oxLDL, which was additionally associated with improvement of stenosis in patients with carotid atheromatosis. We thus, assume that oxLDL may represent a far more sensitive risk factor for carotid stenosis, than LDL itself or apoB. Further studying is required to confirm such findings and to establish a clear clinical and pathophsiologic link between oxLDL and carotid stenosis.

6. Acknowledgment

7. References

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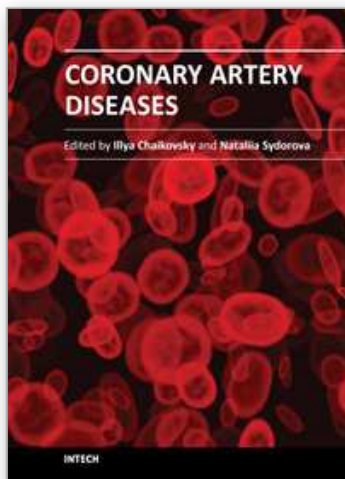
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Coronary Artery Diseases

Edited by Dr. Illya Chaikovsky

This book has "wide geography" both literally and figuratively. First of all, this book brings together contributions from around the world, both from post-industrial countries and developing world. This is natural, because coronary artery disease is becoming pandemic worldwide. CAD is the single most frequent cause of death in developed countries, causes about 1 in every 5 deaths. Mortality from cardiovascular disease is predicted to reach 23.4 million in 2030. Moreover, in the developing world, cardiovascular disease tends to affect people at a younger age and thus could negatively affect the workforce and economic productivity. The morbidity, mortality, and socioeconomic importance of CAD make its diagnosis and management fundamental for all practicing physicians. On another hand, the book widely represents "geography" of CAD itself, i.e. many various aspects of its pathophysiology, epidemiology, diagnosis, treatment are touched in this book. This book does not pretend on complete and integral description of the Coronary artery disease. Rather, it contains selected issues on this complex multifactorial disease. Nevertheless, we hope that readers will find Coronary Artery Disease useful for clinical practice and further research.

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