

Plasma Oxidized Low-Density Lipoprotein, a Strong Predictor for Acute Coronary Heart Disease Events in Apparently Healthy, Middle-Aged Men From the General Population

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Background—Oxidized LDL (oxLDL) is thought to play a key role in the inflammatory response in the arterial vessel wall.

Methods and Results—In a prospective, nested, case-control study, the association between plasma oxLDL and risk of an acute coronary heart disease (CHD) event was investigated in men without prevalent CHD or diabetes mellitus at baseline. Subjects came from 2 population-based MONICA/KORA Augsburg surveys conducted in the years 1989–1990 and 1994–1995 with follow-up in 1998 (mean±SD follow-up time, 5.6±2.6 years). OxLDL was determined by ELISA in 88 men with incident CHD and in 258 age- and survey-matched controls. Hazard ratios (HRs) were estimated from conditional logistic-regression models with matching for age and survey. Baseline mean plasma oxLDL concentrations were significantly higher in subjects who subsequently experienced an event compared with controls (mean±SD, 110±32 versus 93±28 U/L; $P\leq 0.001$). After adjustment for smoking, hypertension, obesity, physical activity, education, and alcohol consumption, the HR for a future CHD event in a comparison of the upper tertile of the oxLDL distribution with the lower tertile was 4.25 (95% confidence interval, 2.09 to 8.63; $P<0.001$).

Plasma oxLDL was the strongest predictor of CHD events compared with a conventional lipoprotein profile and other traditional risk factors for CHD. When both oxLDL and C-reactive protein were simultaneously assessed in the same model, they still predicted future CHD events even after multivariable adjustment.

Conclusions—Elevated concentrations of oxLDL are predictive of future CHD events in apparently healthy men. Thus, oxLDL may represent a promising risk marker for clinical CHD complications and should be evaluated in further studies. (*Circulation*. 2005;112:651-657.)

Key Words: lipoproteins ■ inflammation ■ coronary disease ■ metabolism ■ risk factors

Hypercholesterolemia represents a major risk factor for atherosclerosis.¹ However, atherosclerosis is a multifactorial disease,² and subjects with familial hypercholesterolemia, who have high LDL cholesterol concentrations since birth, nevertheless show considerable variation in the expression of clinical disease. This suggests that other factors modulate the impact of hypercholesterolemia on the arterial vessel wall, increasing or decreasing the pace at which atherosclerosis progresses.³

Several studies have provided strong evidence that an acute coronary syndrome (ACS) is triggered by activation of the immune system-mediated inflammatory process associated with atherothrombosis.^{4–6} Because oxidized (ox) LDL has been detected in plasma of coronary heart disease (CHD) patients,^{7–9} it might play a key role in the generation of inflammatory processes in atherosclerotic lesions of all stages.¹⁰

It has also been shown that oxLDL is involved in the very early yet critical steps of atherogenesis, such as endothelial injury, expression of adhesion molecules, and leukocyte recruitment and retention, as well as foam cell and thrombus formation.^{11–13}

The aim of the present prospective, nested, case-control study therefore was to determine whether plasma oxLDL concentrations predict risk of acute CHD events. Furthermore, we sought to investigate whether measurement of plasma oxLDL in addition to a standard lipid profile and C-reactive protein (CRP), a sensitive marker of inflammation, might add to improved prediction of CHD risk.

Methods

Study Design, Study Sample, and Follow-Up

A prospective, nested, case-control design was used to assess the association between plasma concentrations of oxLDL and risk of an

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acute CHD event. Subjects came from 2 population-based MONICA (MONItoring of trends and determinants in CArdiovascular disease) Augsburg surveys conducted in 1989–1990 and 1994–1995. The MONICA Augsburg project was part of the multinational WHO MONICA project.^{14,15} Altogether, 9796 men and women aged 25 to 74 years participated in the 2 independent cross-sectional surveys (1989–1990 survey, 4940 subjects; 1994–1995 survey, 4856 subjects). In a follow-up study in 1998, vital status was assessed for all sampled persons in the 2 surveys. During follow-up, 89 men without prevalent CHD or diabetes mellitus at baseline developed an acute coronary event (1989–1990 survey, 78 cases; 1994–1995 survey, 11 cases). For each case, 3 age- and survey-matched control subjects were randomly selected from the 2 surveys, resulting in a study sample of 356 subjects (89 cases, 267 controls). We decided not to include women because of their very low event rate. The age-adjusted means and proportions of covariates for incident cases and controls in the present study sample corresponded to that for participants of the source sample. Therefore, the study sample used in this case-control design was representative of the total cohort. Because 10 men with missing data for any of the considered parameters had to be excluded from analysis, the study sample comprised 88 cases and 258 controls.

The outcome variable was a combination of incident fatal or nonfatal acute myocardial infarction (MI) and sudden cardiac death. They were identified through the MONICA/KORA (Kooperative Gesundheitsforschung in der Region Augsburg) coronary event registry of the 25- to 74-year-old study population and censored at the 75th year of age. According to the MONICA manual, the diagnosis of a major nonfatal MI was based on symptoms, cardiac enzymes, and typical ECG changes. Deaths from cardiovascular causes were validated by autopsy reports, death certificates, chart review, and information from the last treating physician.

Data Collection

Information on history of disease, smoking habits, medication use, and alcohol consumption was gathered by trained medical staff during a standardized interview. In addition, all participants underwent a medical examination. All measurement procedures had been standardized and are described in detail elsewhere.¹⁶ Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Obesity was defined as a BMI ≥ 30 kg/m². Persons being aware of having hypertension, taking antihypertensive medication, and/or having blood pressure values $\geq 140/90$ mm Hg at baseline were defined as hypertensives. Leisure-time physical activity was assessed on a 4-level graded scale for winter and summer.¹⁷ The number of education years was calculated on the basis of the highest level of formal education completed.

Laboratory Procedures

A nonfasting venous blood sample was obtained from all study participants in a sitting position. Total serum cholesterol (TC) was measured by an enzymatic method (CHOD-PAP, Boehringer Mannheim). The coefficient of variation for repeatedly measured duplicates was 1.1%. HDL cholesterol (HDL-C) was also measured enzymatically after precipitation of the apoprotein B-containing lipoproteins with phosphotungstate/Mg²⁺ (Boehringer Mannheim). Concentrations of CRP and oxLDL were measured in stored samples (frozen at -80°C) in each case in a single analytical run. The interval between blood draw and a CHD event ranged from 1.3 to 91.9 months. Serum CRP concentrations were determined with a high-sensitivity immunoradiometric assay (range, 0.05 to 10 mg/L) as previously described.¹⁸ The coefficient of variation for repeated measurements was 12% for all ranges. Plasma concentrations of oxLDL were measured by a commercially available competitive sandwich ELISA (Mercodia; interassay coefficient of variation, 15.6%) with the same specific murine monoclonal antibody, mAb-4E6, as in the assay described by Holvoet et al.⁸ It has been shown that oxLDL remains stable in stored samples and that the aforementioned assay has good reproducibility.¹⁹

Statistical Analysis

Statistical associations of continuous variables with categorical variables were assessed by *t* test (2 categories) or *F* test (>2 categories); in case of nonnormality, the Mann-Whitney *U* test was used to analyze group differences. The χ^2 test was used to examine associations between categorical variables, and Pearson correlation was used to assess associations between continuous variables. To evaluate the impact of each lipid parameter on the risk of a coronary event during follow-up, separate conditional logistic-regression models were calculated with matching for age and survey. Each lipid parameter was divided into 3 categories (lower, middle, and upper tertiles) with the distribution thirds as cutoff points. Hazard ratios (HRs) comparing the middle and upper tertiles with the lower tertile are reported together with their 95% confidence intervals (CIs). All lipid and lipoprotein markers followed approximately a normal distribution. Adjustment was made for educational level (<12 years, ≥ 12 years), smoking status (never-smoker, former smoker, current regular or occasional smoker), alcohol consumption (no, 1 to 40 g/d, >40 g/d), physical activity (inactive, active), obesity (no, yes), and hypertension (no, yes). To estimate the discriminative value of the different prediction models, we calculated Akaike's information criterion (AIC) with regard to an AIC difference between 2 models (ΔAIC) of >10 as essentially different.^{20,21} Moreover, receiver-operating characteristic analyses were used to estimate the ability of a conditional logistic regression model to discriminate between subjects with and without a coronary event. For comparing the areas under 2 receiver-operating characteristic curves (AUCs) of 2 models, the method of DeLong et al²² was used. For all statistical analyses, a probability value <0.05 was considered statistically significant. All computations were performed with the statistical software package SAS (version 8.02 for Unix; SAS Institute, Inc).

Results

For all subjects in the case-control study ($n=346$), the mean follow-up time from baseline to development of an acute CHD event was 5.6 years (SD, 2.6). For study participants in the 1989–1990 survey, it was 6.0 years (SD, 2.4) and for participants in the 1994–1995 survey, it was 2.6 years (SD, 1.0). Baseline characteristics of men who subsequently had an acute CHD event (cases) and those who remained free of an event (controls) are shown in Table 1. As expected, men with an event had significantly higher mean BMI and had a higher prevalence of smoking and hypertension. The proportion of those being physically active and the distribution of daily alcohol consumption were similar between the 2 groups. The prevalence of lipid-lowering drug and aspirin medication use was low, with 6 participants using fibrates (2 cases, 4 controls), 1 participant using statins (0 case, 1 control), and 18 using aspirin (11 cases, 7 controls).

Baseline plasma concentrations of oxLDL were significantly higher among men who had an acute CHD event than among those who did not (Table 2). Similarly, baseline levels of TC, LDL-C, non-HDL-C, and the TC/HDL-C ratio were significantly higher among men with subsequent events than in those without. Levels of HDL-C were somewhat lower among men with events than among control subjects, but these differences were not statistically significant.

Table 3 shows that in both cases and controls, oxLDL was related to TC, LDL-C, non-HDL-C, and the TC/HDL-C ratio. In controls, oxLDL was also significantly related to age, BMI, physical activity, hypertension, and HDL-C. There was no significant correlation between oxLDL and CRP in cases and only a barely significant association in controls. Neither

TABLE 1. Demographic and Clinical Characteristics of CHD Patients and Controls

Characteristics	CHD Patients (n=88)	Controls (n=258)	<i>P</i>
Follow-up time,* y	3.2±2.3	6.4±2.1	<0.001
Age,* y	61.1±8.6	61.3±8.4	0.859
Education (<12 y)†	76.1	75.2	0.859
Body mass index,* kg/m ²	28.6±4.0	27.7±3.7	0.049
Hypertension† (≥140/90 mm Hg)	76.1	56.2	0.001
Physical activity††	31.8	29.1	0.626
Smoker†			0.018
Never	21.6	31.4	
Former	42.0	46.9	
Current	36.4	21.7	
Alcohol intake,† g/d			0.959
0	18.2	17.8	
1–40	55.7	57.4	
>40	26.1	24.8	

*Arithmetic mean±SD, *P* value from *t* test.

†Percentage, *P* value from χ^2 test.

‡Regular participation in sports in summer and winter and for at least 1 hour per week in either season.

in cases nor in controls was oxLDL correlated with smoking or alcohol consumption.

Among all lipid variables, oxLDL was the most powerful predictor of risk in multivariable analysis (HR for men in the upper tertile compared with the lower tertile was 4.25; 95% CI, 2.09 to 8.63; *P*<0.001; Table 4). The HR between the highest compared with the lowest category for TC and LDL-C was 1.92 and 2.38, respectively. For HDL-C, the HR in the upper category was 0.69. Moreover, for non-HDL-C, the HR for a CHD event was 2.18 in the upper category compared with the lower category. Among conventional lipid variables, the TC/HDL-C ratio was one of the most powerful predictors of CHD risk (HR, 2.32; 95% CI, 1.23 to 4.37). The HRs comparing the middle tertile with the lower tertile were not significant for each lipid parameter, ranging between 0.69 (for HDL-C) and 1.83 (for oxLDL). Despite HDL-C, the HRs

TABLE 2. Laboratory Characteristics of CHD Patients and Controls (n=346)

Characteristics	CHD Patients (n=88)	Controls (n=258)	<i>P</i>
Total cholesterol,* mg/dL	257±42	243±42	0.012
HDL cholesterol,* mg/dL	50±15	52±15	0.254
TC/HDL ratio*	5.5±1.6	5.0±1.8	0.020
Non-HDL cholesterol,* mg/dL	207±43	192±42	0.004
LDL cholesterol,* mg/dL	171±39	157±40	0.005
Oxidized LDL,* U/L	110±32	93±28	<0.001
CRP (n=320),† mg/L	2.8±3.2	1.7±3.0	<0.001

*Mean±SD, *P* value from *t* test.

†Geometric mean±GSD, *P* value from *t* test for log-transformed characteristic; n=320 (81 cases/239 noncases).

To convert values for total cholesterol, HDL cholesterol, LDL cholesterol, and non-HDL cholesterol to millimoles per liter, divide by 38.66.

TABLE 3. Association Between OxLDL and Other Cardiovascular Risk Factors in CHD Patients and Controls by Pearson Correlation Coefficient *r* and Mean±SD With *P* Values

Risk Factor	OxLDL			
	CHD Patients (n=88)		Controls (n=258)	
	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>
Total cholesterol*	0.737	<0.001	0.610	<0.001
HDL cholesterol*	−0.084	0.437	−0.130	0.037
TC/HDL ratio*	0.519	<0.001	0.391	<0.001
Non-HDL cholesterol*	0.751	<0.001	0.658	<0.001
LDL cholesterol*	0.694	<0.001	0.666	<0.001
CRP*‡	0.142	0.204	0.129	0.046
Age*	−0.127	0.240	0.193	0.002
BMI*	−0.093	0.390	0.162	0.009
Education†		0.460		0.161
<12 y	108±31		91±29	
≥12 y	114±36		97±26	
Hypertension†		0.637		0.040
No	113±34		89±29	
Yes	109±32		96±27	
Physical activity†		0.521		0.001
No	111±30		97±28	
Yes	107±36		84±27	
Smoker†		0.348		0.713
Never	101±34		95±27	
Former	113±33		92±28	
Current	111±30		93±29	
Alcohol intake,† g/d		0.672		0.665
0	103±35		91±30	
1–40	111±33		92±28	
>40	111±29		95±28	

*Pearson correlation coefficient.

†Mean±SD of oxLDL, *P* value from *t* test and *F* test, respectively.

‡26 Missing values.

were always intermediate. For HDL-C, the HRs for the middle and upper tertiles compared with the lower tertile were almost equal (Table 4). No substantial differences in HRs were observed by replacing obesity with BMI and hypertension with systolic blood pressure in the multivariable models.

Moreover, we assessed whether the predictive value of oxLDL was additive to other risk factors for CHD (Table 4). We compared models containing education, smoking status, alcohol consumption, physical activity, obesity, and hypertension with models that in addition included oxLDL or each of the conventional lipid variables. With regard to AIC values, an Δ AIC of 14.56 indicated a substantial improvement in the prediction of a coronary event by including oxLDL in addition to other cardiovascular risk factors. Also, the AUC increased from 0.654 for the model without oxLDL to 0.722 with oxLDL (*P*=0.012). The AUC for the model with oxLDL was higher than for models that had included other lipid variables in addition. Only the TC/HDL-C ratio

TABLE 4. Effects of OxLDL and Different Lipid Variables on the Incidence of an Acute CHD Event, Adjusted for Various Cardiovascular Risk Factors*

Model	HR† (95% CI)	HR‡ (95% CI)	ΔAIC	AUC	P§
No lipid marker*	0	0.654	...
Oxidized LDL	1.83 (0.89–3.78)	4.25 (2.09–8.63)	14.56	0.722	0.012
Total cholesterol	1.22 (0.63–2.34)	1.92 (1.02–3.60)	0.47	0.680	0.119
HDL cholesterol	0.69 (0.37–1.28)	0.69 (0.37–1.29)	–2.11	0.675	0.074
TC/HDL ratio	1.28 (0.65–2.51)	2.32 (1.23–4.37)	3.57	0.703	0.009
Non-HDL cholesterol	1.24 (0.64–2.39)	2.18 (1.17–4.06)	2.81	0.695	0.037
LDL cholesterol	1.53 (0.77–3.01)	2.38 (1.25–4.52)	3.48	0.690	0.064

*Education, smoking status, alcohol consumption, physical activity, obesity, and hypertension.

†Hazard ratio comparing the medium third vs the low third of the distribution of lipid markers.

‡Hazard ratio comparing the high third vs the low third of the distribution of lipid markers.

§P value for difference of AUC for model without lipid marker and model with lipid marker according to DeLong et al.²²

Tertile cutpoints: oxLDL 84.2, 108.0; TC 228.1, 260.8; HDL-C 44.4, 56.1; TC/HDL-C ratio 4.4, 5.5; non-HDL-C 175.4, 208.9; and LDL-C 141.6, 175.1.

ΔAIC: Difference of AIC of model without lipid marker and model with lipid marker.

revealed a significant improvement of prediction in addition to the other cardiovascular risk factors (0.703 versus 0.654, $P=0.009$).

Furthermore, we investigated whether oxLDL would predict future CHD events independent of CRP and TC/HDL-C. Analyses were restricted to 320 persons (81 cases and 239 controls) because of missing data for CRP. When assessed in a separate model (Figure 1), CRP was a powerful predictor in multivariable analysis (HR for men in the upper tertile compared with the lower tertile was 2.64; 95% CI, 1.23 to 5.66; $P=0.013$). The corresponding value for oxLDL was 3.02 (95% CI, 1.33 to 6.86; $P=0.008$; Figure 2). When oxLDL and CRP were simultaneously assessed in the same model, both parameters still predicted future CHD events, even after multivariable adjustment. The HR for the upper versus the lower tertile was slightly stronger for oxLDL (2.79; 95% CI, 1.21 to 6.42; $P=0.016$) than for CRP (2.30;

95% CI, 1.06 to 5.02; $P=0.036$; Figure 2). The joint effects of plasma oxLDL and CRP on the incidence of a coronary event were also tested by including interaction terms in the model. No significant interactions occurred between oxLDL and CRP ($P=0.647$).

However, oxLDL did not significantly increase the prediction of a coronary event. After inclusion of oxLDL in a model containing CRP, the TC/HDL-C ratio, and all other cardiovascular risk factors, the additional improvement in risk prediction was rather low: the AUC increased nonsignificantly, from 0.700 (model without oxLDL) to 0.716 (model with oxLDL). Furthermore, the ΔAIC value between both models was 2.63 (data not shown).

Discussion

In this nested, case-control study in apparently healthy subjects randomly drawn from a general population with a

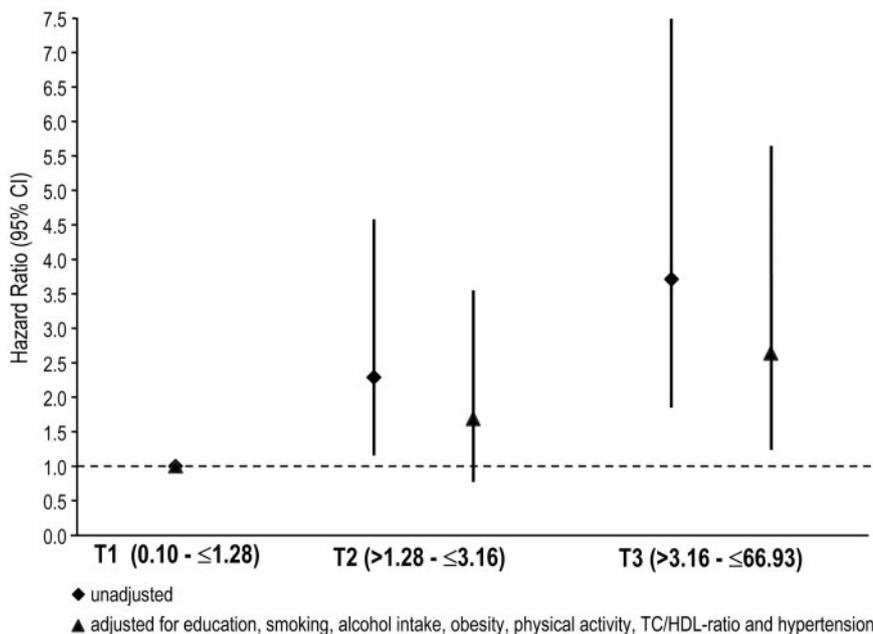


Figure 1. Relative risks (hazard ratios) of CHD events, according to tertile (T1, T2, T3) of CRP (mg/L) concentrations at baseline. Reference category is T1; n=320. Filled diamond is unadjusted value. Filled triangle is value adjusted for education level, smoking status, alcohol intake, obesity, physical activity, TC/HDL-C ratio, and hypertension.

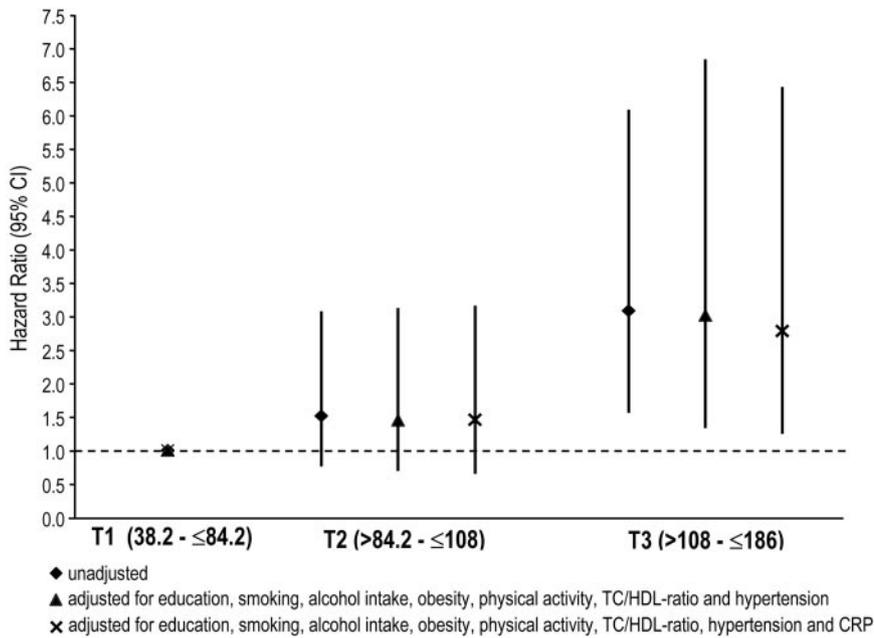


Figure 2. Relative risks (hazard ratios) of CHD events according to tertiles (T1, T2, T3) of oxLDL (U/L) concentrations at baseline. Reference category is T1; n=320. Filled diamond is unadjusted value. Filled triangle is value adjusted for education level, smoking status, alcohol intake, obesity, physical activity, TC/HDL-C ratio, and hypertension. Multiplication sign is value adjusted for education level, smoking status, alcohol intake, obesity, physical activity, TC/HDL-C ratio, hypertension, and CRP value.

moderate absolute risk of CHD, for the first time we demonstrate a strong association between oxLDL and future CHD events. Our findings suggest that oxLDL is a stronger predictor of risk than standard lipid variables and other traditional CHD risk factors. Furthermore, when both oxLDL and CRP were simultaneously assessed in the same model, they still predicted future coronary events, even after adjustment for all traditional cardiovascular risk factors and the TC/HDL-C ratio, one of the most powerful predictors of risk among conventional lipid variables. Thus, circulating oxLDL in plasma may be a useful additional marker to identify subjects at risk of CHD.

To date, a number of case-control studies have examined the involvement of oxidative modifications of LDL in subjects with the presence of clinical cardiovascular disease. Holvoet et al⁸ demonstrated elevated plasma concentrations of oxLDL in patients with stable CHD or ACSs compared with age-matched, apparently healthy controls. Ehara et al²³ reported that oxLDL concentrations were significantly higher in patients with MI than in patients with unstable or stable angina pectoris or age-matched control subjects, suggesting a positive association between oxLDL and the severity of ACSs. Furthermore, Holvoet et al⁷ also showed that oxLDL was correlated with the extent of coronary artery disease (CAD) in heart transplant recipients. In a further case-control study,⁹ 65 patients with prevalent CHD were compared with 181 normal subjects and 102 patients with non-insulin-dependent diabetes mellitus without a history of CHD. Concentrations of oxLDL in patients with angiographically proven CAD were 1.9-fold higher than in age-matched controls.⁹ Findings from another study suggested that plasma levels of oxLDL represent a more sensitive marker for the presence of CAD than the Global Risk Assessment Score, although a significant association between oxLDL and most of the Framingham risk factors was observed.²⁴

Salonen et al²⁵ in 1992 were the first to conduct a prospective, population-based, nested, case-control study in

which the titers of autoantibodies to malondialdehyde-modified LDL and native LDL in baseline serum samples from 30 Finnish men with accelerated progression of carotid atherosclerosis were compared with 30 age-matched controls without progression during a 2-year follow-up. They found titers of autoantibodies to oxLDL to predict progression of carotid atherosclerosis. Since then, one small, prospective, nested, case-control study indicated that elevated oxLDL concentrations may be associated with subsequent acute MI. During a follow-up of 2.6 years, 26 cases and 26 matched controls and an additional 26 controls with LDL-C >5.0 mmol/L were studied. The oxLDL/plasma cholesterol ratio was higher among cases compared with controls and also higher compared with hypercholesterolemic subjects free of an event, suggesting that the high plasma oxLDL/TC ratio might serve as a possible indicator of increased risk of MI.²⁶ However, in that study, the clinical utility of oxLDL was not compared with other conventional CHD risk factors or CRP, which has been consistently shown to be associated with increased risk of MI.^{27,28}

Only recently has an association between the metabolic syndrome and a high prevalence of oxLDL been found in a population-based cohort of individuals aged 70 to 79 years at baseline. In that study, participants with high oxLDL concentrations had a greater risk of future CHD (relative risk, 2.25; 95% CI, 1.22 to 4.15), defined as coronary death or any hospitalization for MI, angina, coronary angioplasty, coronary artery bypass grafting, or chronic heart failure. However, oxLDL was not an independent predictor of incident CHD risk in that study.²⁹

The clinical relevance of oxLDL measurement in apparently healthy, middle-aged men has not been established so far. Thus, the results of our study have several important implications. We convincingly showed that the measurement of oxLDL discriminated men who subsequently developed an acute CHD event from those who remained event-free, even after adjustment for major CHD risk factors. Thus, these data

support the hypothesis that the presence of elevated plasma concentrations of oxLDL may contribute to the clinical manifestation of CHD. Although oxLDL can be directly measured in blood, it seems unlikely that it is produced in the circulation because of the abundance of antioxidants in plasma.³⁰ Hence, high oxLDL concentrations in plasma might reflect its release from atheromatous plaque. In the present study, there was no correlation between oxLDL and CRP in men with an acute coronary event, suggesting that both markers are not completely involved in the same pathophysiological pathway in the atherosclerotic disease process. Atherosclerosis is a chronic inflammatory condition that is converted to an acute coronary event by induction of plaque rupture or fissure.^{6,27,28} CRP, the classic acute-phase protein, though a sensitive marker of inflammation,⁴ may be involved in the pathogenesis of atherosclerosis in several ways,^{31,32} whereas oxLDL, being a prominent autoantigen, might play an important role in the activation of adaptive immunity and/or in the induction of the cellular inflammatory response. Indeed, it has been shown that Th1 lymphocytes, the pivotal cells of the adaptive immune reaction, recognize oxLDL, and oxLDL in turn may activate them to produce strong local responses in the plaque.^{33,34} In addition, immunization with oxLDL^{35–37} as well as IgG treatment³⁸ has been shown to reduce atherosclerosis in various animal models.

Furthermore, elevated oxLDL could play a role in the transition from stable to vulnerable, unstable plaque, because plaques prone to rupture usually consist of a lipid-rich core and abundant inflammation in the plaque cap. This may ultimately lead to erosion, fissure, or overt rupture, with subsequent thrombotic occlusion of the vessel lumen.³⁹ Nishi et al⁴⁰ reported that LDL undergoes further oxidation in plaque and that high concentrations of oxLDL in plasma and plaque are correlated with the vulnerability of atherosclerotic lesions. The assumption that oxLDL may not only contribute to the initiation and progression of atherosclerosis but also directly promote plaque rupture is supported by 2 recent studies showing that oxLDL stimulates matrix metalloproteinase (MMP)-1 and -9 expression in human vascular endothelial cells⁴¹ and in monocyte-derived macrophages,⁴² enzymes that are directly involved in promoting plaque destabilization. Also, Li et al⁴³ showed that oxLDL upregulates the expression of MMP-1 and -3 in human coronary artery endothelial cells. These effects of oxLDL were mediated through its endothelial receptor LOX-1, a novel lectinlike receptor for oxLDL. Furthermore, oxLDL through its receptor LOX-1 triggers the CD40/CD40L signaling pathway, which may lead to an inflammatory reaction and endothelial injury.⁴⁴ These findings are supported by the fact that inhibition of LOX-1 reduced ischemic injury in animal models.⁴⁵

Several limitations of the present study need to be considered. Because the study was limited to middle-aged men of German nationality, caution should be used in generalizing these results to women, other populations, ethnic/racial minorities, and other age-groups. Despite adjustment for a variety of confounders, the associations observed in the present study could be due to confounding by unmeasured variables. Moreover, we could not adjust for blood glucose.

Thus, our findings clearly need to be validated in other cohorts. So far, oxLDL is not a clinically available laboratory biomarker. Standardization of assays, sensitivity, specificity, positive predictive value, negative predictive value, and cost-benefit issues will need to be determined before oxLDL can be embraced as a clinically useful screening tool.

In conclusion, increased plasma concentrations of oxLDL are predictive of future CHD events in apparently healthy, middle-aged men from a population with moderate absolute risk. The association is independent of the conventional lipoprotein profile, other traditional risk factors for CHD, and CRP. Thus, the additional measurement of oxLDL may improve prediction of atherosclerotic CHD complications.

Further studies are warranted to establish the clinical relevance of oxLDL measurement in various stages of the atherosclerotic process and to identify the specific pathophysiological mechanisms by which oxLDL exerts its deleterious effects.

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