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Value of Low-Density Lipoprotein Particle Number and Size as Predictors of Coronary Artery Disease in Apparently Healthy Men and Women

The EPIC-Norfolk Prospective Population Study

Karim El Harchaoui, MD,* Wim A. van der Steeg, MD,* Erik S. G. Stroes, MD, PHD,* Jan Albert Kuivenhoven, PHD,* James D. Otvos, PHD,‖ Nicholas J. Wareham, MBBS, PHD,‡ Barbara A. Hutten, PHD,† John J. P. Kastelein, MD, PHD,* Kay-Tee Khaw, MBBCHIR,§ S. Matthijs Boekholdt, MD, PHD*

Amsterdam, the Netherlands; Cambridge, United Kingdom; and Raleigh, North Carolina

Objectives We assessed relations of low-density lipoprotein (LDL) particle number (LDL-P) and LDL particle size as measured by nuclear magnetic resonance spectroscopy with LDL cholesterol (LDL-C) and the risk of future coronary artery disease (CAD).

Background Whereas LDL-C is an established risk factor for CAD, its discriminative power is limited. Measuring LDL-P and size may have stronger associations with CAD than LDL-C.

Methods A nested case-control study was performed in the prospective EPIC (European Prospective Investigation into Cancer and Nutrition)-Norfolk study, which comprises 25,663 subjects. Cases (n = 1,003) were individuals who developed CAD during 6 year follow-up. Control subjects (n = 1,885) were matched for age, gender, and enrollment time. Odds ratios (ORs) for future CAD were calculated, and we also evaluated whether LDL-P could improve the Framingham risk score (FRS) to predict CAD.

Results In univariate analyses, LDL-P (OR 2.00, 95% confidence interval [CI] 1.58 to 2.59) and non-high-density lipoprotein cholesterol (non–HDL-C) (OR 2.14, 95% CI 1.69 to 2.69) were more closely associated with CAD than LDL-C (OR 1.73, 95% CI 1.37 to 2.18). The additional value of LDL-P was lost after adjustment for HDL-C and triglyceride levels. Whereas LDL size was inversely related to CAD (OR 0.60, 95% CI 0.47 to 0.76), this relation was abolished upon adjustment for LDL-P. In a model adjusted for the FRS, LDL-P retained its association with CAD (p for trend 0.02).

Conclusions In this large study of individuals with moderately elevated LDL-C, LDL-P was related to CAD on top of FRS as well as after adjusting for LDL-C. The additional value of LDL-P was comparable to non–HDL-C, and it was abolished after adjusting for triglycerides and HDL-C. (J Am Coll Cardiol 2007;49:547–53) © 2007 by the American College of Cardiology Foundation

The causal role of low-density lipoprotein (LDL) particles in the pathogenesis of coronary artery disease (CAD) is well established, as is the clinical benefit of lowering LDL in high-risk patients. Hence, low-density lipoprotein-cholesterol (LDL-C) lowering is the principal target in cardiovascular preventive strategies (1). Low-density lipoprotein cholesterol content is used as a parameter to estimate LDL-associated CAD risk. More recently, assessment of the number of LDL particles has been put forward as a more reliable method reflecting atherogenicity of the LDL fraction (2). Since the cholesterol content per LDL particle exhibits large inter-individual variation due to differences in particle size as well as relative content of cholesterol ester and triglycerides in the particle core, the information provided by LDL-C and low-density lipoprotein-particle number (LDL-P) is not equivalent (3).

From the Departments of *Vascular Medicine and †Clinical Epidemiology and Biostatistics, Academic Medical Centre, University of Amsterdam, Amsterdam, the Netherlands; ‡Medical Research Council Epidemiology Unit, Cambridge, United Kingdom; §Department of Public Health and Primary Care, Institute of Public Health, University of Cambridge, Cambridge, United Kingdom; and ‖LipoScience Inc., Raleigh, North Carolina. Dr. Otvos is an employee of LipoScience, Inc.

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Abbreviations and Acronyms

apoB = apolipoprotein B
BMI = body mass index
CAD = coronary artery disease
CI = confidence interval
FRS = Framingham risk score
HDL-C = high-density lipoprotein cholesterol
LDL = low-density lipoprotein
LDL-C = low-density lipoprotein cholesterol
LDL-P = low-density lipoprotein-particle number
NMR = nuclear magnetic resonance
OR = odds ratio

Individuals with the same level of LDL-C may have higher or lower numbers of LDL particles and, as a result, may differ in terms of absolute CAD risk. Prospective studies, in which LDL particle concentration was estimated by apolipoprotein B (apoB) levels, have underscored stronger associations between LDL-P and CAD risk compared with LDL-C, particularly in subjects with normal LDL-C concentration (4,5). In addition, the size of LDL particles may also contribute to the atherogenicity of LDL-C (6,7). Thus, at a given level of LDL-C, individuals with small LDL particles have greater atherosclerotic risk than those with large-size LDL (8,9).

Lipoprotein particle analysis by nuclear magnetic resonance (NMR) spectroscopy is a relatively new method by which both LDL-P and LDL particle size can be efficiently measured (10). We evaluated the associations between LDL-P and LDL size, in comparison with LDL-C and non–high-density lipoprotein cholesterol (non–HDL-C) as traditional markers, and risk of future CAD in apparently healthy men and women enrolled in a large prospective cohort with moderately elevated LDL-C. Since LDL-P and LDL size are closely related to traditional lipid factors such as HDL-C and triglycerides, we performed multivariable analyses to assess independency of the correlations. We also assessed clinical usefulness of these novel parameters by determining their effect on the discriminative accuracy of the Framingham risk score (FRS).

Methods

We performed a nested case-control study among participants of the EPIC (European Prospective Investigation into Cancer and Nutrition)-Norfolk study, a prospective population study of 25,663 men and women aged between 45 and 79 years, resident in Norfolk, United Kingdom, who completed a baseline questionnaire survey and attended a clinic visit (11). Participants were recruited from age-gender registers of general practices in Norfolk as part of the 10-country collaborative EPIC study designed to investigate dietary and other determinants of cancer. Additional data were obtained in the EPIC-Norfolk study to enable the assessment of determinants of other diseases.

The design and methods of the study have been described in detail (11). In short, eligible participants were recruited by mail. At the baseline survey between 1993 and 1997, participants completed a detailed health and lifestyle questionnaire. Non-fasting blood was taken by vein puncture into plain and citrate bottles. Blood samples were processed for assay at the Department of Clinical Biochemistry, University of Cambridge, or stored at −80°C. All individuals were flagged for death certification at the United Kingdom Office of National Statistics, with vital status ascertained for the entire cohort. In addition, participants admitted to hospital were identified using their unique National Health Service number by data linkage with ENCORE (East Norfolk Health Authority) database. Coronary artery disease was defined as codes 410-414 according to the International Classification of Diseases-9th revision. Participants were identified as having CAD during follow-up if they had a hospital admission and/or died with CAD as underlying cause. We report results with follow-up up to January 2003, an average of about 6 years. The study was approved by the Norwich District Health Authority Ethics Committee, and all participants gave signed informed consent.

Participants. We excluded all individuals who reported a history of heart attack or stroke at the baseline clinic visit. None of the cases or control subjects was on statin treatment. Cases were individuals who developed a fatal or non-fatal CAD during follow-up. For each case, 2 control subjects matched for gender, age (within 5 years), and time of enrollment (within 3 months) were identified who had remained free of CAD during follow-up.

NMR spectroscopy. Lipoprotein subclass particle concentrations and average size of LDL particles were measured by proton NMR spectroscopy (LipoScience, Inc., Raleigh, North Carolina) as previously described (10). Particle concentrations of lipoprotein subclasses of different size were obtained directly from the measured amplitudes of their spectroscopically distinct lipid methyl group NMR signals. The following LDL subclasses were defined: intermediate-density lipoprotein (IDL) (23 to 27 nm), large LDL (21.2 to 23 nm), and small LDL (18 to 21.2 nm). Low-density lipoprotein subclass particle concentrations are given in units of nmol/l. Summation of the LDL subclass levels provides total LDL (including intermediate-density lipoprotein) particle concentrations. Weighted-average LDL particle sizes (in nm diameter units) are computed as the sum of the diameter of each subclass multiplied by its relative mass percentage as estimated from the amplitude of its methyl NMR signal. Low-density lipoprotein subclass distributions determined by NMR and gradient gel electrophoresis are highly correlated (12). Low-density lipoprotein subclass diameters, which are consistent with electron microscopy data (13), are uniformly ~5 nm smaller than those estimated by gradient gel electrophoresis.

Biochemical analyses. Serum levels of total cholesterol, HDL-C, and triglycerides were measured with the RA 1000 (Bayer Diagnostics, Basingstoke, United Kingdom), and LDL-C levels were calculated with the Friedewald formula (14). Nuclear magnetic resonance analysis was performed on stored serum samples that were analyzed in random order to avoid systemic bias. Researchers and

laboratory personnel were blinded to identifiable information, and could identify samples by number only.

Statistical analysis. Baseline characteristics were compared between cases and controls taking into account the matching. A mixed effect model was used for continuous variables, and conditional logistic regression was used for categoric variables. Because triglyceride levels had a skewed distribution, values were log-transformed before being used as continuous variables in statistical analyses.

Spearman correlation coefficients and corresponding p values were calculated to assess associations between the various biomarkers and established continuous CAD risk factors. To assess the strength of association between a risk factor and the occurrence of CAD, we calculated odds ratios (ORs) and corresponding 95% confidence intervals (CIs) by conditional logistic regression analysis, taking into account matching for gender, age, and enrollment time. The ORs were calculated per quartile of each risk factor, with the first quartile as the referent group. P values represent significance for linearity across the ORs for the 4 quartiles of each risk factor. To compare the individual strengths of disease association of LDL-P, non–HDL-C, LDL-C, HDL-C, and triglycerides, we calculated ORs for future CAD per quartile of each variable in separate models adjusted for smoking (yes/no) and systolic blood pressure. Since our objective was to determine relations of lipids/lipoproteins with CAD, we did not adjust additionally for body mass index (BMI) and diabetes, 2 lipid-altering risk factors. Multivariable models were also examined to determine how relations of each variable were affected by adjustment for the other lipid/lipoprotein variables.

We further assessed the relation of LDL-P and non–HDL-C with future CAD using a model that included the FRS. We calculated this score using a previously reported algorithm (15) based on age, gender, levels of total and HDL cholesterol, systolic and diastolic blood pressure, diabetes, and smoking and categorized subjects into 3 groups: low (<10%), intermediate (10% to 20%), or high (>20%) risk. The ORs for future CAD were calculated per quartile of the risk factor, adjusting for the FRS category.

Statistical analyses were performed using SPSS software (version 12.0.1, SPSS Inc., Chicago, Illinois). A p value <0.05 was considered to indicate statistical significance.

Results

Baseline characteristics. We identified 1,003 participants who were apparently healthy at baseline and developed CAD during follow-up. A total of 882 cases were matched to 2 controls each, whereas the remaining 121 cases could be matched to 1 control only, giving a total number of 1,885 controls. Baseline characteristics of cases and controls are listed in Table 1. As expected, cases were more likely to be smokers and diabetic subjects, and to have a higher blood pressure and BMI than control subjects. Levels of total cholesterol, LDL-C, non–HDL-C, and triglycerides were significantly higher in cases than in control subjects, whereas HDL-C levels were significantly lower ($p < 0.0001$ for each). Baseline LDL-P was higher in cases compared with control subjects ($p < 0.0001$). Levels of the large LDL subclass were not different, but cases had more IDL

Table 1 Baseline Characteristics of Coronary Artery Disease Cases and Matched Control Subjects

	Control Subjects (n = 1,885)	Cases (n = 1,003)	p Value
Male gender, % (n)	63.2 (1,192)	63.9 (641)	Matched
Age, yrs	65 ± 8	65 ± 8	Matched
Diabetes, % (n)	1.6 (30)	6.1 (61)	<0.0001
Smoking, % (n)	8.3 (155)	15.7 (157)	<0.0001
BMI, kg/m^2	26.2 ± 3.4	27.3 ± 3.9	<0.0001
Systolic blood pressure, mm Hg	139 ± 18	144 ± 19	<0.0001
Diastolic blood pressure, mm Hg	84 ± 11	86 ± 12	<0.0001
Chemical lipid measures			
Total cholesterol, mmol/l	6.2 (5.5–6.9)	6.4 (5.6–7.2)	<0.0001
HDL cholesterol, mmol/l	1.3 (1.1–1.6)	1.2 (1.0–1.8)	<0.0001
LDL cholesterol, mmol/l	4.0 (3.4–4.7)	4.2 (3.6–4.9)	<0.0001
Triglycerides, mmol/l	1.6 (1.1–2.2)	1.8 (1.3–2.6)	<0.0001
Non-HDL cholesterol, mmol/l	4.8 (4.1–5.6)	5.2 (4.4–5.9)	<0.0001
NMR LDL particle measures			
LDL particle number, nmol/l	1,525 (1,278–1,812)	1,640 (1,383–1,955)	<0.0001
IDL, nmol/l	36 (14–66)	43 (19–78)	0.003
Large LDL, nmol/l	572 (448–704)	568 (427–708)	0.6
Small LDL, nmol/l	885 (637–1,190)	999 (747–1,330)	<0.0001
LDL size, nm	21.1 (20.7–21.5)	21.0 (20.1–21.4)	0.002

Data are presented as mean ± SD, percentage (n), or median (interquartile range). Means, percentages, and medians may be based on fewer observations than the indicated number of subjects. Triglyceride levels were log-transformed before analysis.

BMI = body mass index; HDL = high-density lipoprotein; IDL = intermediate-density lipoprotein; LDL = low-density lipoprotein; NMR = nuclear magnetic resonance.

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Table 2 Spearman Correlation Coefficients Between Measured Variables*

	Non-HDL Cholesterol	LDL Cholesterol	LDL Particle Number	LDL Size
LDL cholesterol	0.94			
LDL particle number	0.76	0.63		
LDL size	−0.18	0.01†	−0.58	
Total cholesterol	0.94	0.93	0.65	
HDL cholesterol	−0.16	−0.03‡	−0.29	0.54
Triglycerides	0.47	0.18	0.55	−0.53
BMI	0.11	0.02§	0.14	−0.19

*$p < 0.0001$ for comparison unless otherwise indicated; †$p = 0.6$; ‡$p = 0.09$; §$p = 0.2$.
BMI = body mass index; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

and small LDL particles. Thus, the increased LDL-C in cases is attributable mainly to increased cholesterol in small LDL. The average LDL particle size was smaller in cases than control subjects.

Associations of LDL measures with other CAD risk factors. As shown in Table 2, LDL size was inversely correlated with LDL-P ($r = -0.58$), but not with LDL-C ($r = 0.01$). We identified a strong inverse relation of LDL size with triglyceride levels ($r = -0.53$) and BMI ($r = -0.19$) and a positive correlation with HDL-C ($r = 0.54$). Both LDL-C and LDL-P were strongly interrelated ($r = 0.63$), but both parameters had markedly different associations with HDL-C and triglycerides. Whereas LDL-C was only weakly associated with HDL-C ($r = -0.03$) and triglyceride levels ($r = 0.18$), LDL-P was more strongly correlated with HDL-C ($r = -0.29$) and triglycerides ($r = 0.55$). Non–HDL-C was strongly correlated with LDL-P ($r = 0.76$) and triglycerides ($r = 0.47$), and inversely correlated with HDL-C ($r = -0.16$) and LDL size ($r = -0.18$).

LDL-P, traditional lipid risk factors, and risk for future CAD. Shown in the upper panel of Table 3 are the univariate ORs for future CAD associated with increasing quartiles of non–HDL-C, LDL-C, LDL-P, HDL-C, and triglycerides. The 5 lipid/lipoprotein measures exhibited comparable strengths of association with CAD, with ORs differing approximately 2-fold comparing the highest and lowest quartiles. The magnitude of the predictive value of LDL-P and non–HDL-C were greater than that of LDL-C. Comparing the highest to lowest quartile, the OR for LDL-P was 2.00 (95% CI 1.58 to 2.59) and 2.14 (95% CI 1.69 to 2.69) for non–HDL-C versus 1.73 (95% CI 1.37 to 2.18) for LDL-C.

The lower panels of Table 3 show the results of multivariate analyses in which each lipid/lipoprotein variable was adjusted for the other 2 parameters to assess the independence of their mutual relations with CAD. The associations of both LDL-C and LDL-P with CAD were attenuated after adjustment for HDL-C and triglycerides, whereas attenuation was more pronounced for LDL-P than for LDL-C (4th quartile ORs reduced from 2.00 to 1.37 for LDL-P vs. 1.73 to 1.55 for LDL-C). Similarly, relations of HDL-C and triglycerides with CAD were attenuated more by adjustment for LDL-P than LDL-C.

Concordance/discordance between LDL-C and LDL-P. In a conditional logistic regression model that included both parameters and corrected for smoking and systolic blood

Table 3 Odds Ratios for Future Coronary Artery Disease by Quartile of Lipid/Lipoprotein Variable in Univariable and Multivariable Models*

	Quartiles				
	1	2	3	4	p Value†
Univariable models					
LDL cholesterol	1.00	1.37 (1.09–1.73)	1.38 (1.09–1.74)	1.73 (1.37–2.18)	<0.0001
LDL particle number	1.00	1.23 (0.97–1.56)	1.48 (1.17–1.87)	2.00 (1.58–2.59)	<0.0001
HDL cholesterol	1.00	0.76 (0.60–0.95)	0.60 (0.48–0.75)	0.50 (0.39–0.64)	<0.0001
Triglycerides	1.00	1.27 (1.00–1.62)	1.50 (1.20–1.88)	2.01 (1.61–2.51)	<0.0001
Non-HDL cholesterol	1.00	1.31 (1.04–1.66)	1.57 (1.25–1.97)	2.14 (1.69–2.69)	<0.0001
Multivariable models					
LDL cholesterol	1.00	1.26 (0.99–1.60)	1.27 (1.00–1.61)	1.55 (1.22–1.96)	0.001
HDL cholesterol	1.00	0.83 (0.66–1.04)	0.71 (0.56–0.89)	0.66 (0.50–0.87)	0.001
Triglycerides	1.00	1.12 (0.88–1.43)	1.22 (0.96–1.54)	1.52 (1.19–1.95)	0.001
LDL particle number	1.00	1.13 (0.89–1.44)	1.21 (0.94–1.54)	1.37 (1.04–1.83)	0.02
HDL cholesterol	1.00	0.86 (0.68–1.09)	0.74 (0.59–0.94)	0.70 (0.53–0.92)	0.005
Triglycerides	1.00	1.11 (0.87–1.42)	1.19 (0.93–1.51)	1.36 (1.04–1.79)	0.03
Non-HDL cholesterol	1.00	1.13 (0.88–1.44)	1.26 (0.99–1.62)	1.63 (1.26–2.11)	<0.0001
HDL cholesterol	1.00	0.83 (0.66–1.05)	0.71 (0.56–0.90)	0.66 (0.50–0.87)	0.001
Triglycerides	1.00	1.08 (0.85–1.39)	1.13 (0.88–1.43)	1.30 (0.99–1.70)	0.06

*Odds ratios (95% confidence intervals) were calculated by conditional logistic regression, taking into account matching for gender, age, and enrollment time and adjusted additionally for smoking and systolic blood pressure. Univariable models examined each lipid/lipoprotein variable in a separate model. Multivariable models examined each variable in a model adjusted for the other 2 lipid/lipoprotein variables as continuous variables. †p for linear trend.
Abbreviations as in Table 2.

Table 4 Odds Ratios for Future Coronary Artery Disease by Quartile of LDL-C and LDL-P, Both Entered Into One Model*

	LDL Size Quartile				
	1	2	3	4	p Value†
LDL-C	1.00	1.23 (0.97–1.57)	1.13 (0.88–1.45)	1.22 (0.92–1.61)	0.3
LDL-P	1.00	1.18 (0.93–1.51)	1.39 (1.08–1.79)	1.78 (1.34–2.37)	<0.0001

*Odds ratios (95% confidence intervals) were calculated by conditional logistic regression adjusted for smoking and systolic blood pressure; †p for linear trend.
LDL-C = low-density lipoprotein cholesterol; LDL-P = low-density lipoprotein particle number.

pressure, LDL-C was no longer statistically significantly associated with future CAD (Table 4). The LDL-P, however, remained a significant risk factor, such that subjects in the highest quartile had an OR of 1.78 (95% CI, 1.34 to 2.37; $p < 0.0001$ for linearity) (Table 4).

LDL size and risk for future CAD. Table 5 shows the ORs for future CAD associated with increasing quartiles of LDL size adjusted for smoking and systolic blood pressure, with and without additional adjustment for the potentially confounding inverse correlation of LDL size with LDL-P. Without adjustment for LDL-P, there was a significant relation of smaller LDL size with CAD, with an OR for individuals in the highest quartile compared with those in the lowest quartile of 0.60 (95% CI 0.47 to 0.76). However, upon adjustment for LDL-P, the relation of LDL size with CAD was greatly attenuated and was no longer significant.

LDL-P and the FRS. The results in Table 6 indicate that LDL-P and non–HDL-C retain a similar association with future CAD after accounting for the FRS (OR of 1.34 and 1.38, respectively, in the highest vs. lowest quartile).

Discussion

Measurements of LDL-P and LDL size have the potential to improve coronary disease risk assessment as well as decisions about LDL treatment intensity, since they account for aspects of lipid atherogenicity that are incompletely reflected by values of LDL-C. In this large prospective case-control study, we show that LDL-P and non–HDL-C were more closely associated with the occurrence of future CAD than levels of LDL-C. Upon adjusting for HDL-C and triglyceride levels, the predictive capacity of LDL-P was comparable to that of LDL-C. Whereas LDL size was related to CAD risk, this relationship was abolished after adjusting for LDL-P. Both LDL-P and non–HDL-C had incremental value on top of the FRS in multivariate analyses. Overall, these findings do not support routine use of LDL-P for CAD risk assessment in primary prevention setting.

LDL-P and risk for future CAD. The cholesterol content of LDL particles, which can create discordance between levels of LDL-C and LDL-P, is mainly influenced by cholesterol ester transfer protein activity, which is enhanced under circumstances of hypertriglyceridemia (8). This has 2 important consequences. First, transfer of cholesteryl ester from HDL particles to apoB-containing lipoproteins causes low HDL-C levels. Second, cholesterol depletion and triglyceride enrichment of LDL particles facilitates the formation of small dense LDL particles (3,8). As a result, LDL-C levels generally underestimate the number of LDL particles in individuals with elevated triglycerides, as clearly illustrated in the Framingham Study (2,3). Discordance between LDL-C and LDL-P is also a feature of diabetic patients (2,16) and the number of metabolic syndrome components (2,17). Our data in the EPIC-Norfolk study showing that triglyceride and HDL-C levels are much more strongly correlated with LDL-P than LDL-C are in agreement with these findings. Accordingly, it was not unexpected that the relation of LDL-P with CAD risk was to be weakened more than that of LDL-C by multivariate adjustment for triglycerides and HDL-C. Conversely, adjusting for LDL-P weakened relations of CAD with triglycerides and HDL-C, suggesting that some of the risk associated with these non-LDL risk factors may actually stem from elevations of LDL-P not reflected by levels of LDL-C.

We found a moderate degree of discordance between LDL-C and LDL-P in our study population. While the source of this excess risk may not be due entirely to the elevated LDL-P, since those with discordantly high LDL-P

Table 5 Odds Ratios for Future Coronary Artery Disease by Quartile of LDL Size, With and Without Adjustment for LDL Particle Number*

	LDL Size Quartile				
	1	2	3	4	
Range (nm)	<20.6	20.7–21.0	21.1–21.4	>21.4	p Value†
Unadjusted for LDL particle number	1.00	0.77 (0.62–0.97)	0.76 (0.60–0.95)	0.60 (0.47–0.76)	<0.0001
Adjusted for LDL particle number	1.00	0.92 (0.72–1.16)	0.99 (0.77–1.28)	0.86 (0.65–1.15)	0.5

*Odds ratios (95% confidence intervals) were calculated by conditional logistic regression adjusted for smoking and systolic blood pressure, with and without additional adjustment for low-density lipoprotein (LDL) particle number; †p for linear trend.

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Table 6 Odds Ratios for Future Coronary Artery Disease After Taking Into Account the Framingham Risk Score*

	Quartiles				
	1	2	3	4	p Value†
LDL cholesterol	1.00	1.17 (0.93–1.48)	1.09 (0.86–1.39)	1.24 (0.97–1.58)	0.15
LDL particle number	1.00	1.10 (0.86–1.39)	1.22 (0.96–1.54)	1.34 (1.03–1.73)	0.02
Non-HDL cholesterol	1.00	0.98 (0.73–1.32)	1.03 (0.76–1.38)	1.38 (1.01–1.90)	0.04

*Odds ratios were calculated by conditional logistic regression, with adjustment for risk categories based on the Framingham risk score; †p for linear trend.

Abbreviations as in Table 2.

often have increased triglycerides and decreased HDL-C, it is biologically plausible that LDL-P makes a contribution. Current understanding of the pathophysiology of atherosclerotic vascular disease is that LDL particles are active participants from the time they enter the artery wall, are retained in the intima by binding to extracellular matrix, become chemically modified by oxidation, and are subsequently ingested by macrophages to create foam cells and increased plaque burden (2,4).

Despite the finding that LDL-P predicted CAD independently of the FRS, our results, showing a loss of discriminative power of LDL-P over LDL-C when HDL-C and triglyceride levels are accounted for, do not argue for the routine implementation of LDL-P assessment for CAD risk assessment. Low-density lipoprotein cholesterol particle number may, however, play a useful role in patient management by helping judge the adequacy of LDL lowering therapy, particularly among those with elevated triglycerides and reduced HDL-C. Such a role has been proposed for apoB (4,5), and both non–HDL-C and apoB have been put forward as secondary treatment targets after LDL-C goals have been achieved (1,4). In fact, data supporting LDL-P as an alternative treatment target has gained support from clinical intervention studies showing that on-treatment levels of apoB or NMR-measured LDL-P were more reliable indicators of residual CAD risk than on-treatment LDL-C (2,4,5,18,19).

LDL size and risk for future CAD. Small LDL size is another factor associated with high triglycerides, low HDL-C, obesity, insulin resistance, diabetes, and metabolic syndrome (6–9). Our finding of a relation between smaller LDL size and greater CAD risk is consistent with previous studies reporting that small LDL particles have higher atherogenic potential than large LDL particles (8,9). However, upon adjustment for LDL-P, the relationship of LDL size with CAD was abolished. This result is consistent with findings in the Multi-Ethnic Study of Atherosclerosis indicating that NMR-measured numbers of small and large LDL particles are related similarly to carotid atherosclerosis (20).

Non–HDL-C and risk for future CAD. The present findings confirm that non–HDL-C is a better predictor of CAD than LDL-C (21,22). Previous studies have also found that the number of most atherogenic lipoprotein particles, as measured by apoB, were more strongly related to CAD risk than was non–HDL-C (21,22). In the present study, we show that the association of LDL-P with CAD is almost equal to that of non–HDL-C. The fact that apoB captures all atherogenic apoB particles (including very low-density lipoprotein and LDL), whereas LDL-P only measures LDL particles, may have contributed to this distinction. There has been an intense debate concerning clinical relevance of measuring particle numbers (apoB/LDL-P) and/or cholesterol content of the particles (non–HDL-C). In the present study, we observed that both LDL-P as well as non–HDL-C conferred predictive value on top of the FRS. Since the association between LDL-P and CAD was equal to that of non–HDL-C, the present findings do not advocate routine use of LDL-P in CAD risk assessment. The potential value of LDL-P measurement for monitoring patients on lipid-lowering medication needs to be addressed in separate intervention trials.

Study limitations. Our study has several limitations. The study population was relatively elderly, which may limit the generalizability of our results. Case-control differences in CAD among older populations are more weakly related to lipoprotein levels than in younger populations because many of the control subjects have extensive subclinical disease, yet have not experienced a coronary event (23). Low-density lipoprotein cholesterol levels in the study population were also considerably higher than in the general U.S. population, with a mean LDL-C value in the EPIC-Norfolk study corresponding to the 80th percentile of Framingham subjects of similar age and gender (24). Coronary artery disease events in our study were ascertained through death certification and hospital admission data, which may lead both to under ascertainment and to misclassification of cases. Previous validation studies in this cohort, however, indicate high specificity of such case ascertainment (25).

In conclusion, in this large cohort of apparently healthy men and women, LDL-P and non–HDL-C were more closely associated than LDL cholesterol with the occurrence of future CAD. After adjustment for HDL-C and triglycerides, LDL-P was no longer more predictive than LDL-C. These findings do not support routine use of LDL-P in CAD risk assessment strategies in primary prevention strategies. However, recognition that patients with low HDL-C and/or high triglycerides often have elevated numbers of LDL particles without having elevated LDL-C may enable their LDL-related CAD risk to be managed more effectively.

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Reprint requests and correspondence: Dr. John J. P. Kastelein, F4.159-2, Department of Vascular Medicine, Academic Medical Centre, Meibergdreef 9, 1105 AZ Amsterdam, the Netherlands. E-mail: j.j.kastelein@amc.uva.nl.

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