Smallest LDL Particles Are Most Strongly Related to Coronary Disease Progression in Men

Paul T. Williams, H. Robert Superko, William L. Haskell, Edwin L. Alderman, Patricia J. Blanche, Laura Glines Holl, Ronald M. Krauss

Objective—LDLs include particle subclasses that have different mobilities on polyacrylamide gradient gels: LDL-I (27.2 to 28.5 nm), LDL-IIa (26.5 to 27.2 nm), LDL-IIb (25.6 to 26.5 nm), LDL-IIIa (24.7 to 25.6 nm), LDL-IIIb (24.2 to 24.7 nm), LDL-IVa (23.3 to 24.2 nm), and LDL-IVb (22.0 to 23.3 nm in diameter). We hypothesized that the association between smaller LDL particles and coronary artery disease (CAD) risk might involve specific LDL subclasses.

Methods and Results—Average 4-year onstudy lipoprotein measurements were compared with annualized rates of stenosis change from baseline to 4 years in 117 men with CAD. The percentages of total LDL and HDL occurring within individual subclasses were measured by gradient gel electrophoresis. Annual rate of stenosis change was related concordantly to onstudy averages of total cholesterol ($P=0.04$), triglycerides ($P=0.05$), VLDL mass ($P=0.03$), total/HDL cholesterol ratio ($P=0.04$), LDL-IVb ($P=0.01$), and HDL$_{3a}$ ($P=0.02$) and inversely to HDL$_{2}$-mass ($P=0.02$) and HDL$_{2b}$ ($P=0.03$). The average annual rate in stenosis change was 6-fold more rapid in the fourth quartile of LDL-IVb ($≥5.2\%$) than in the first quartile ($<2.5\%$, $P=0.03$). Stepwise multiple regression analysis showed that LDL-IVb was the single best predictor of stenosis change.

Conclusions—LDL-IVb was the single best lipoprotein predictor of increased stenosis, an unexpected result, given that LDL-IVb represents only a minor fraction of total LDL. (Arterioscler Thromb Vasc Biol. 2003;23:314-321.)

Key Words: lipoproteins • coronary disease • risk factors • LDL • HDL

Human plasma LDLs include multiple distinct subclasses of different particle size that are separable on nondenaturing polyacrylamide gradient gels.$^1$ Seven LDL subclasses have been identified: LDL-I (27.2 to 28.5 nm), LDL-IIa (26.5 to 27.2 nm), LDL-IIb (25.6 to 26.5 nm), LDL-IIIa (24.7 to 25.6 nm), LDL-IIIb (24.2 to 24.7 nm), LDL-IVa (23.3 to 24.2 nm), and LDL-IVb (22.0 to 23.3 nm in diameter).$^1,2$ Several case-control, nested case-control, and prospective studies have suggested that a predominance of smaller LDL particles (ie, LDL-III or LDL-IV) is associated with increased coronary heart disease (CHD) risk.$^3,10$ The contribution of individual subclasses within LDL-III and LDL-IV to CHD risk has not been determined.

HDLs also include a heterogeneous mixture of particles of differing size that can be separated into at least 5 subclasses on nondenaturing polyacrylamide gradient gels.$^{11}$ These include HDL$_{3a}$ (7.2 to 7.8 nm), HDL$_{3b}$ (7.8 to 8.2 nm), HDL$_{4a}$ (8.2 to 8.8 nm), HDL$_{4b}$ (8.8 to 9.7 nm), and HDL$_{5}$ (9.7 to 12 nm).$^{11}$ Case-control and angiographic studies suggest that CHD risk may be increased when HDL$_{2}$ is reduced relative to HDL$_{3a}$ and HDL$_{3b}$.12-14

The rate at which coronary artery lesions progress is a risk factor for clinical coronary events. The rate of change in percent stenosis has been shown to be significantly predictive of myocardial infarctions and coronary deaths during 7-year$^{15}$ and 12-year$^{16}$ follow-up periods. The rate is also reflective of atherosclerosis elsewhere, eg, changes in carotid artery intima-media thickness.$^{17}$ Quantitative changes in coronary artery diameters and stenosis have been associated with plasma levels of total cholesterol,$^{18}$ LDL cholesterol,$^{18,19}$ HDL cholesterol,$^{20,21}$ HDL$_{2}$ cholesterol,$^{20}$ HDL$_{2b}$,$^{20}$ LDL density,$^{22-24}$ apolipoprotein B (apo B),$^{18}$ lipoprotein(a) [Lp(a)],$^{18,25}$ triglyceride-rich lipoprotein remnants,$^{21}$ and hepatic lipase activity.$^{24}$

The purpose of this study was to examine the relations of LDL and HDL subclasses to rates of CHD progression. Specifically, average onstudy measurements of lipoprotein subclasses were compared with annual rates of stenosis change of coronary lesions in men who remained under care of their usual physician when serving as controls in a randomized trial.$^{26}$ The analyses show that the annual rate of progression of coronary artery stenosis is related to the relative levels of specific LDL and HDL subclasses. Consistent with other reports,$^{22,27}$ we found preliminary evidence that effects of lipoproteins on atherosclerotic progression may be related to baseline lesion severity.
Methods

Study Design
The Stanford Coronary Risk Intervention Project (SCRIP) was a 4-year, randomized, controlled clinical trial of the efficacy of multifactor risk reduction for reducing CHD progression.26 It included a control group that remained under care of their own usual physicians during the 4-year period. The control arteriograms at baseline and after 4 years and the lipoprotein subclass measurements taken during the intervening 4 years provide the data for this report. Eligible participants were recruited between February 1984 and March 1987 for the 4-year intervention trial. They were required to be <75 years old and free of severe congestive heart failure, pulmonary disease, intermittent claudication, or noncardiac life-threatening illness. After arteriography, patients were treated medically, received percutaneous transluminal coronary angioplasty, or had coronary artery bypass graft surgery, in accordance with standard clinical indications. Subjects remained eligible for the study if (1) at least 1 major coronary artery had a segment with luminal narrowing between 5% and 69% that was unaffected by the revascularization procedures and (2) the left ventricular ejection fraction was at least 20%. Randomization into treatment or control (usual care) conditions occurred after baseline evaluations (however, data from the control group only are analyzed in this report). All subjects were scheduled for 4 annual medical and risk-factor evaluations and a follow-up coronary arteriography at the fourth year. The study protocol and progress reports were reviewed before the start of the study and annually thereafter by the Stanford University Panel on Human Subjects in Medical Research and the Committee for the Protection of Human Subjects at the University of California. Because men and women have different LDL profiles28 and the number of female subjects in SCRIP was small (n=29), only men were analyzed in the current report. This study was carried out in full compliance with the University of California and Stanford University Committee for the Protection of Human Subjects.

Quantitative Arteriography
Arteriograms were made by the patient’s attending physician using a uniform protocol. Specifically, these used catheters with metallic size markers, prior nitroglycerin administration, and replication of projection angles.26 Follow-up arteriograms were obtained within a 6-week window of the patient’s fourth-year anniversary of his baseline arteriogram. The segment quantifications on baseline and follow-up films used identical projections from the single plane that best visualized each segment. An automatic edge-finding algorithm defined the edges of the calibrating catheter and the coronary vessels.26 A reference diameter was defined to compute percent stenosis in diseased segments.

All assessable portions of the coronary vessels >1.5 mm in diameter on the baseline arteriograms were divided into 0.5- to 3.5-cm segments. Qualifying segments had to have clearly quantifiable lumen margins and along with the proximal vessel, could not contain lesions having 70% or greater diameter reduction. Vessels that had been grafted or instrumented by a prior revascularization procedure were also excluded. To ensure comparable measurements of the quantification segments on serial arteriograms, segments were defined by either proximal or distal fiducial points and by absolute length. Clinically mandated coronary arteriograms obtained during the study were performed under this same protocol. When a vessel containing a qualifying segment was affected by a subsequent revascularization procedure, the quantification results for that segment up to the last available preprocedure arteriogram were then used. Qualifying segments that were totally occluded on follow-up arteriography were coded as 100% stenosis, and segments distal to total occlusion were considered lost to follow-up.

Lipid, Lipoprotein, Glucose, and Insulin Measurements
At baseline and annually thereafter, fasting plasma lipids were measured at 2 clinic visits, usually within 2 weeks of each other. The 2 values were averaged for each subject to represent the subject at baseline and for each year in the study. Plasma concentrations of total cholesterol and triglycerides were measured by enzymatic procedures (ABA 200 instrument, Abbott Laboratories).19 HDL cholesterol was measured by the dextran sulfate–magnesium precipitation of apo B–containing lipoproteins, and the remainder of plasma was used for the enzymatic determination of cholesterol.20,21 The laboratory remained certified by the Centers for Disease Control and Prevention Lipid Standardization Program throughout the study. Lp(a) and LDL plus IDL in apo B d>1.006 g/mL lipoproteins were separated by ultracentrifugation,32 and the infranatant was collected and stored at −70°C for subsequent analysis by ELISA.33,34 Plasma glucose concentration was measured with the glucose oxidase method, and insulin concentration, by radioimmunossay26 after an overnight fast and 1 hour after administration of a 100-g oral glucose load.

Electrophoresis of LDL in whole plasma and HDL in the d<1.20 g/mL fraction was performed on a Pharmacia electrophoresis apparatus (GE 4-II Pharmacia) and slab gradient gels (PAA 2/16 and PAA 4/30, respectively; Pharmacia).1,2 Lipid staining for LDL was performed by incubating the gels overnight in a 50°C to 60°C oven, and 0.61 g oil red O stain. Protein-stained gels for HDL were obtained by agitating the gels in a 50- to 75-mL solution of 0.04% Coomassie G-250 and 3.5% perchloric acid after fixing the protein in 10% sulfosalicylic acid for 1 hour. The gels were scanned with a model RPT densitometer (Transidyne Corp) at wavelengths of 555 nm for the lipid-stained gels and 603 nm for the protein-stained gels.1 Analyses are based on the percentage of the total LDL (22.0 to 28.5 mm) and HDL (7.2 to 12.0 nm) represented by each subclass. Analytic ultracentrifugation was used to measure concentrations of total lipoprotein mass within multiple regions for HDL, (F1,40 to 3.5), LDL, (F3,5.3 to 9), small LDL (S,0 to 7), large LDL (S,7 to 12), IDL (S,12 to 20), and VLDL mass concentrations (S,20 to 40).35

One hundred seventeen of the 139 men (84%) randomized to receive their usual physician’s care had follow-up arteriograms. These occurred, on average, (mean±SD), 3.97±0.45 years after their baseline arteriogram. Exposure of the arteries to lipoproteins was estimated by averaging plasma lipoprotein values for all available clinic visits. Nearly all subjects had lipid and lipoprotein measurements available at all 5 annual visits (1 man had data from 4 visits and 2 men had data from 3 visits). A decision was made not to collect plasma for detailed lipoprotein subtraction and subclass measurements at the third annual visit. From the remaining 4 clinic visits, all available data were used to compute onstudy averages for analytic ultracentrifuge measurements of lipoprotein mass (4 annual visits in 101 men, 3 visits in 13 men, and 2 visits in 3 men) and gradient gel measurements of LDL subclasses (4 visits in 95 men, 3 visits in 19 men, and 2 visits in 3 men). The analyses of gradient gel estimates of LDL subclasses are limited to baseline and fourth-year data from 106 men.

Statistical Analysis
The annual rate of stenosis change was averaged for all diseased segments within each individual. Least-squares regression was used to test for significant associations between the annual rate of stenosis change (the dependent variable) and the onstudy average lipoprotein, body mass index, resting heart rate, and blood pressure levels (the independent variables) during the 4-year study. Multiple regression analysis was used to test for a significant association between the rate of stenosis change and average percent LDL–IVB after adjustment for other onstudy measurements, and stepwise regression analysis was used to select the best regression model for predicting change in stenosis. Significant associations were verified by the nonparametric Spearman rho. An ANOVA test for trend was used to test for increasing (or decreasing) mean annual rate of stenosis when the observations were partitioned by quartiles of the average onstudy lipoprotein levels. We also tested whether baseline levels of stenosis affected the relations of onstudy lipoproteins to the annualized rate of stenosis change. The 364 diseased segments were separated into 2 categories (184 segments each) according to whether or not baseline stenosis was less than the median (median=30% stenosis). Within each category, the change in the rate of stenosis was averaged for all
qualifying segments within each individual. There were 96 men with 1 or more diseased segments with <30% stenosis at baseline (mean ± SD, 21.81 ± 4.79%) and 86 men with 1 or more diseased segments with 30% or greater stenosis at baseline (mean ± SD, 39.39 ± 6.16%). The annual rate of stenosis change was not related in the segments having <30% and those having ≥30% stenosis at baseline (r = 0.09, P = 0.46 in 65 men having both types of segments). All significance levels are 2-sided.

Results

Table 1 presents the characteristics of the sample. On average, the men were in their fifth decade, moderately over-
weight, mostly nonhypertensive, and had only moderately elevated plasma lipids. Forty-two men (35.9%) had average LDL cholesterol levels ≥160 mg/dL, and 20 men (17.1%) had average HDL cholesterol levels <35 mg/dL. Twelve men were hypertensive, as defined by either systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg. Eighteen men had average onstudy fasting plasma glucose concentrations >7.0 mmol/L. During the study, only 12% of the men ever took bile acid–binding resins, 13.7% ever took niacin, 8.5% ever took fibric acid compounds, and only 7.7% ever took a 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor.

The annualized rate of stenosis change from baseline to 4 years was unrelated to average onstudy smoking status (P=0.99), daily cigarette consumption (P=0.68), heart rate (P=0.95), systolic blood pressure (P=0.75), diastolic blood pressure (P=0.77), body mass index (P=0.06), treadmill test duration (P=0.91), and postchallenge insulin (P=0.13) and glucose (P=0.10) concentrations in plasma. Table 2 shows that the rate of stenosis change was significantly related to fasting glucose (P=0.0008) and insulin (P=0.02). The association between stenosis and onstudy fasting glucose was significant for the 18 men with onstudy glucose ≥7.0 mmol/L (slope±SE, 0.53±0.20, P=0.02) but not for the 90 men with levels <7.0 mmol/L (0.15±0.36, P=0.67).

Table 2 also presents the regression slopes relating annual rates of stenosis change to average onstudy plasma lipid and lipoprotein concentrations and percent distributions of LDL and HDL subclasses. Average plasma concentrations of total cholesterol and triglycerides and the average ratio of total cholesterol to HDL cholesterol were all related concordantly to the annual rate of stenosis change. Although the inverse relation between plasma HDL cholesterol concentrations and rate of stenosis change failed to achieve statistical significance (P=0.11), average HDL2b levels were inversely related to annual rates of stenosis change (P=0.03). Average LDL cholesterol and small-LDL mass (ie, S0 to 7) also failed to achieve statistically significant concordant relations with the annual rate of stenosis change. However, rates of stenosis change were associated significantly with onstudy averages for the percentages of total LDL within the LDL-IVb interval (P=0.01) and marginally with onstudy averages for LDL-IIIb (P=0.06). Nonparametric Spearman’s correlations confirmed the significant associations of the annual rate of stenosis change with average LDL-IVb (P=0.19, P=0.05), total cholesterol (P=0.25, P=0.008), VLDL mass, and triglycerides (both P=0.19, P=0.04). There was also a significant Spearman correlation between annual rate of stenosis change and plasma concentrations of small-LDL mass averaged over 4 years (P=0.18, P=0.05).

Table 3 presents the regression slopes for the annual rate of stenosis change versus plasma lipoproteins, glucose, and insulin concentrations by baseline stenosis levels. This was done to assess whether (1) the associations observed in Table 2 applied to all segments regardless of the extent of disease and (2) the effects of LDL subclasses on disease progression differed from those of other lipoproteins. In diseased segments with <30% stenosis at baseline, the annual rate of stenosis change was associated concordantly with fasting glucose, LDL-IIIb, and LDL-IVb and inversely with LDL-IIb (Table 3). In diseased segments with ≥30% stenosis at baseline, the annual rate of stenosis change was associated concordantly with fasting glucose and insulin, total cholesterol, total/HDL cholesterol, and HDL3b and inversely with HDL1b and HDL2b (Table 3). Nonparametric Spearman’s correlations confirmed the significant associations of the annual rate of stenosis change with average LDL-IVb (P=0.25, P=0.02) and LDL-IIb (P=0.27, P=0.01) in segments having <30% stenosis at baseline and of the annual rate of stenosis change with total/HDL cholesterol (P=0.21, P=0.05) and HDL3b (P=0.22, P=0.04) in segments having more disease.

Figure 1 displays the mean annual rate of stenosis change by quartiles of LDL-IVb. The cut points were taken at average onstudy LDL-IVb proportions of 2.5%, 3.7%, and 5.2% of total LDL. There was a significant trend for more
rapid stenosis from the first to the fourth quartile ($P=0.04$). The annual rate of stenosis change was 6-fold more rapid in the fourth quartile than in the first quartile of LDL-IVb ($P=0.03$ for difference in means). The association was more pronounced in the segments with <30% stenosis baseline and nonexistent in the segments with greater baseline disease.

Finally, we examined the regression slope between average on-study LDL-IVb and annual rates of stenosis change in all diseased segments when adjusted for other lipoproteins. The association remained significant at $P=0.05$ with only 2 minor exceptions: adjustment for LDL-IIIb and HDL-IVb, each of which reduce the significance levels from $P=0.01$ to $P=0.06$. The relation also persisted when adjusted for body mass index (adjusted slope±SE, 0.208±0.094, $P=0.03$), fasting insulin (0.221±0.092, $P=0.02$), fasting glucose concentrations (0.210±0.090, $P=0.02$), diabetes, and duration of use of bile acid–binding resins, niacin, fibric acid compounds, and HMG CoA reductase inhibitors. The association between annual rates of stenosis change and LDL-IVb remained significant when adjusted for segments with <30% baseline stenosis and remained consistently nonsignificant for segments with greater disease (analyses not displayed).

When stepwise multiple regression analysis was used to select the best-fitting lipoprotein model for predicting the annual rate of stenosis change in all diseased segments, the best model included only 1 variable: average on-study LDL-IVb. Once LDL-IVb was entered into the model, none of the other lipoprotein variables improved prediction of the rate of stenosis change. Including fasting insulin and glucose among the candidate independent variables resulted in the selection

### Table 3: Regression Slopes for Annual Change in Percent Stenosis vs Average On-Study Lipoprotein Measurements in Plasma in Men With High- (>30%) and Low-Percent Stenosis (≤30 percent) at Baseline

<table>
<thead>
<tr>
<th>Lipoprotein Measurement</th>
<th>30% Stenosis at Baseline</th>
<th>30% Stenosis at Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Slope±SE</td>
<td>P</td>
</tr>
<tr>
<td>Fasting glucose, mmol/L</td>
<td>0.287±0.109</td>
<td>0.01</td>
</tr>
<tr>
<td>Fasting insulin, pmol/L</td>
<td>0.001±0.003</td>
<td>0.72</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>0.404±0.263</td>
<td>0.13</td>
</tr>
<tr>
<td>Total cholesterol/HDL-C</td>
<td>0.040±0.199</td>
<td>0.84</td>
</tr>
<tr>
<td>Non-HDL cholesterol, mmol/L</td>
<td>0.357±0.264</td>
<td>0.18</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>0.221±0.268</td>
<td>0.41</td>
</tr>
<tr>
<td>LDL-cholesterol, mmol/L</td>
<td>0.269±0.312</td>
<td>0.39</td>
</tr>
<tr>
<td>HDL-cholesterol, mmol/L</td>
<td>0.754±0.104</td>
<td>0.47</td>
</tr>
<tr>
<td>VLDL-mass, mg/dL</td>
<td>0.002±0.003</td>
<td>0.54</td>
</tr>
<tr>
<td>IDL-mass, mg/dL</td>
<td>0.012±0.014</td>
<td>0.40</td>
</tr>
<tr>
<td>Large LDL-mass, mg/dL</td>
<td>0.005±0.006</td>
<td>0.41</td>
</tr>
<tr>
<td>Small LDL-mass, mg/dL</td>
<td>0.003±0.004</td>
<td>0.44</td>
</tr>
<tr>
<td>HDL$_{IIa}$-mass, mg/dL</td>
<td>0.011±0.008</td>
<td>0.17</td>
</tr>
<tr>
<td>HDL$_{IIb}$-mass, mg/dL</td>
<td>0.000±0.009</td>
<td>0.96</td>
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<tr>
<td>Lp(a), mmol/L</td>
<td>0.187±0.300</td>
<td>0.54</td>
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<tr>
<td>ApoB, g/L</td>
<td>0.763±0.833</td>
<td>0.36</td>
</tr>
<tr>
<td>LDL-peak diameter, nm</td>
<td>0.188±0.361</td>
<td>0.60</td>
</tr>
<tr>
<td>LDL-I, %</td>
<td>0.008±0.048</td>
<td>0.86</td>
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<tr>
<td>LDL-IIa, %</td>
<td>0.003±0.037</td>
<td>0.93</td>
</tr>
<tr>
<td>LDL-IIb, %</td>
<td>-0.103±0.044</td>
<td>0.02</td>
</tr>
<tr>
<td>LDL-IIIa, %</td>
<td>0.012±0.029</td>
<td>0.68</td>
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<tr>
<td>LDL-IIIb, %</td>
<td>0.243±0.101</td>
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<tr>
<td>LDL-IVa, %</td>
<td>0.083±0.188</td>
<td>0.66</td>
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<tr>
<td>LDL-IVb, %</td>
<td>0.326±0.102</td>
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<tr>
<td>HDL-peak diameter, nm</td>
<td>0.016±1.372</td>
<td>0.99</td>
</tr>
<tr>
<td>HDL$_{3a}$, %</td>
<td>-0.004±0.047</td>
<td>0.93</td>
</tr>
<tr>
<td>HDL$_{3b}$, %</td>
<td>-0.051±0.066</td>
<td>0.44</td>
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<tr>
<td>HDL$_{4a}$, %</td>
<td>0.097±0.093</td>
<td>0.30</td>
</tr>
<tr>
<td>HDL$_{4b}$, %</td>
<td>0.070±0.052</td>
<td>0.90</td>
</tr>
<tr>
<td>HDL$_{5a}$, %</td>
<td>-0.031±0.057</td>
<td>0.59</td>
</tr>
</tbody>
</table>

Sample size: 96 men had at least one diseased segment with <30% stenosis at baseline, and 86 men had at least one diseased segment with ≥30% or greater stenosis at baseline. Rates for segments were averaged within each individual.
Mean annual rate of stenosis change of coronary artery lesions by quartiles of mean onstudy LDL-IVb in 106 men. The cut points were taken at average onstudy LDL-IVb proportions of 2.5%, 3.7%, and 5.2%. *Significantly less than the fourth quartile.

Discussion

Although LDL-IVb represents only a minor fraction of lipid-stained LDL (<10%), these analyses suggest that the percentage of LDL contained within this subclass may be the strongest lipoprotein predictor for the annual rate in stenosis change. Total cholesterol, triglycerides, and the ratio of total cholesterol to HDL cholesterol did not predict annual increases in percent stenosis once the effects of LDL-IVb were removed (ie, their nonselection in a stepwise regression analysis). Compared with men in the lowest quartile of LDL-IVb, those in the highest quartile had annual rates of stenosis change of 5% (R=0.22 vs R=0.25).

Of both fasting glucose (P=0.007) and LDL-IVb (P=0.02), When LDL-IVb was excluded from the model, then the best model for predicting the change in stenosis was onstudy HDL-3a, which had a somewhat less fit than LDL-IVb.

The identification of LDL-IVb as the LDL species most strongly related to atherosclerosis progression was unexpected, because onstudy means are likely to be less precise for LDL-IVb than the other lipoprotein measurements. Specifically, the measurement error for an onstudy mean will decrease with the square root of the number of clinic visits used in its calculation. Whereas triglycerides, total cholesterol, and lipoprotein cholesterol were generally calculated as the average for 10 clinic visits and HDL subclasses and analytic ultracentrifuge measurements were calculated as the average of 4 clinic visits, LDL subclasses were calculated for 2 visits only.

There is evidence to suggest that LDL-IVb includes a distinct class of LDL particle that is not simply the “trailing” portions of LDL-IIa or LDL-IIIb. LDL-IVb was initially described on the basis of minor LDL peaks and inflection points appearing within this region. In a previous report involving other male subjects, we identified a number of significant correlations between the LDL-IVb subclass and other lipoprotein parameters. The strengths of these correlations were within the ranges of those observed for the predominant LDL-II and LDL-III subclasses and these lipoproteins. These included significant positive correlations of LDL-IVb with plasma concentrations of triglycerides and apo B. Plasma LDL-IVb levels were also significantly correlated with LDL cholesterol and IDL mass (positively) and with apo A-I and HDL cholesterol (negatively). LDL-IVb was also significantly higher after than before puberty in males and higher after than before menopause in females. In contrast, the intervening subclass, LDL-IVa, showed correlations with other lipoproteins that were weaker than those observed for the flanking LDL-IVb or LDL-IIIb regions and showed no significant difference before and after male puberty or female menopause.

The present findings are consistent with previous studies indicating that smaller peak LDL particle size is predictive of increased risk for myocardial infarction and that angio-
tissue (inversely related to particle size\(^5\)) and prolonged and enhanced retention by the arterial wall (greater in dense than buoyant LDL\(^2\)). Increased postprandial lipemia\(^3\) and increased insulin resistance\(^4\) are also associated with small LDL and may contribute to its atherogenic risk. It remains to be determined, however, whether these mechanisms show a sufficient gradation with LDL size and density to account for LDL-IVb’s apparent atherogenic properties, given its low plasma levels. Albers et al\(^5\) have identified HDL-1 and Lp(a) LDL-IVb’s apparent atherogenic properties, given its low plasma levels. Albers et al\(^5\) have identified HDL-1 and Lp(a) as the aspirant pathogen in the stepwise regression analysis may underestimate its true significance. The provision of standardized measurement of minor LDL-IVb may thus enhance the assessment and management of coronary disease risk.

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### References


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