Lipoprotein-Associated Phospholipase A₂, High-Sensitivity C-Reactive Protein, and Risk for Incident Coronary Heart Disease in Middle-Aged Men and Women in the Atherosclerosis Risk in Communities (ARIC) Study

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Background—Measuring C-reactive protein (CRP) has been recommended to identify patients at high risk for coronary heart disease (CHD) with low LDL cholesterol (LDL-C). Lipoprotein-associated phospholipase A₂ (Lp-PLA₂) is a proinflammatory enzyme associated primarily with LDL.

Methods and Results—In a prospective, case cohort study in 12,819 apparently healthy middle-aged men and women in the Atherosclerosis Risk in Communities study, the relation between Lp-PLA₂, CRP, traditional risk factors, and risk for CHD events over a period of ≈6 years was examined in a proportional hazards model, stratified by LDL-C. Lp-PLA₂ and CRP levels were higher in the 608 cases than the 740 noncases. Both Lp-PLA₂ and CRP were associated with incident CHD after adjustment for age, sex, and race with a hazard ratio of 1.78 for the highest tertile of Lp-PLA₂ and 2.53 for the highest category of CRP versus the lowest categories. Lp-PLA₂ correlated positively with LDL-C (r=0.36) and negatively with HDL-C (r=−0.33) but not with CRP (r=−0.05). In a model adjusted for traditional risk factors including LDL-C, the association of Lp-PLA₂ with CHD was attenuated and not statistically significant. For individuals with LDL-C below the median (130 mg/dL), Lp-PLA₂ and CRP were both significantly and independently associated with CHD in fully adjusted models. For individuals with LDL-C <130 mg/dL, those with both Lp-PLA₂ and CRP levels in the highest tertile were at the greatest risk for a CHD event.

Conclusions—Lp-PLA₂ and CRP may be complementary in identifying individuals at high CHD risk who have low LDL-C. (Circulation. 2004;109:837-842.)

Key Words: coronary disease ■ epidemiology ■ inflammation ■ risk factors

Although screening for elevated LDL cholesterol (LDL-C) remains a major component of national guidelines for the prevention of coronary heart disease (CHD), LDL-C level is insufficient to identify individuals who would develop CHD, because many CHD events occur in individuals without elevated LDL-C, indicating the influence of other risk factors. Inflammation plays an important role in both atherogenesis and atherothrombotic events, and several biomarkers of inflammation, including high-sensitivity C-reactive protein (hs-CRP), interleukin-6, and soluble intercellular adhesion molecule-1, have been associated with increased risk for CHD events. hs-CRP measurement has been recommended for some patients to refine risk assessment because hs-CRP levels have been shown to provide additional predictive information beyond traditional risk factors such as LDL-C. Increased hs-CRP levels may also be useful to identify patients with low LDL-C who are at increased CHD risk and may benefit from statin therapy.

Lipoprotein-associated phospholipase A₂ (Lp-PLA₂) is an enzyme that can hydrolyze oxidized phospholipids to generate lysophosphatidylcholine and oxidized fatty acids, which have proinflammatory properties. However, hydrolysis of platelet-activating factor and other phospholipids by Lp-PLA₂ could also reduce inflammation, and it is not clear whether Lp-PLA₂ is proinflammatory or anti-inflammatory in humans.
Lp-PLA₂ is associated primarily with LDL, and enzyme activity is increased in small, dense LDL.²⁻⁹

In a case–cohort analysis of the West of Scotland Coronary Prevention Study (WOSCOPS), high baseline Lp-PLA₂ levels were associated with increased risk for CHD events, even after adjustment for traditional risk factors and hs-CRP.¹⁰ In a case–control analysis from the Women’s Health Study, baseline Lp-PLA₂ levels were higher in women with subsequent cardiovascular events but were not associated with increased CHD risk after adjustment for traditional risk factors and hs-CRP.¹¹

The purpose of this study was to examine whether levels of Lp-PLA₂ and hs-CRP in middle-aged American men and women were associated with increased risk for incident CHD in the Atherosclerosis Risk in Communities (ARIC) study.

Methods

Study Population

The ARIC design, objectives, sampling strategies, and examination techniques have been described previously.¹² ARIC is a large, biracial cohort study of 15792 adults 45 to 64 years old. A baseline examination was conducted in 1987 to 1989, with 3 more examinations through 1998.

Participants were followed up for incident CHD, defined by combinations of chest pain, ECG changes, cardiac enzyme levels, and surgical revascularization. Potential CHD events were reviewed by 2 members of the ARIC Morbidity and Mortality Classification Committee, and any differences between reviewers were adjudicated by the committee chairperson.

Study Design

Because plasma samples from the first visit were depleted, Lp-PLA₂ and hs-CRP were measured in duplicate in plasma from visit 2 (1990–1992) in individuals who subsequently developed a CHD event (cases) and in a cohort random sample (CRS). Of the 14560 participants with visit 2 data, 1272 were excluded because of CHD or missing CHD information before visit 2, 376 for transient ischemic attack or stroke, and 93 who belonged to an underrepresented minority group. The potential full cohort consisted of 12819 individuals who were followed up for the subsequent development of a CHD event, including CHD-related death. Subjects alive and event-free at the end of 1998 or lost to follow-up were censored. We constructed a case–cohort design (n=1652)¹³ in which cases are compared with a CRS of all participants at the beginning of follow-up. The case–cohort design has the advantages that a single comparison group can be used for multiple disease outcomes (such as incident CHD and stroke), the comparison group is representative of the entire study population, and both absolute risks and relative hazards can be obtained with appropriate statistical analyses.

We selected the CRS by stratification on sex, race (black versus white) and age at baseline (≥55 versus <55). After exclusion of 304 subjects with missing information, the final sample size for the analysis was 1348 (608 cases and 740 noncases). The CRS included 785 individuals: 45 cases and all 740 noncases.

Risk Factor Assessment

Information about medical history, cigarette smoking, and alcohol consumption was based on standardized, validated interviewer-administered questionnaires at visit 2. Body mass index (BMI) was derived from measured height and weight. Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or use of antihypertensive medication in the previous 2 weeks. Diabetes was defined as fasting blood glucose ≥126 mg/dL, nonfasting blood glucose ≥200 mg/dL, a physician’s diagnosis of diabetes, or use of antidiabetic medication in the previous 2 weeks.

Laboratory Measurements

Plasma lipids were measured in centralized laboratories by standard, validated methods reported previously.¹⁴⁻¹⁶ Lp-PLA₂ was assessed by a dual monoclonal antibody immunoassay standardized to recombinant Lp-PLA₂ (PLAC test, diaDexus, Inc.).¹⁷ To assess interassay precision for Lp-PLA₂ measurement, 2 controls of known concentration (low and high) were measured in 40 separate assays. The interassay coefficient of variation on all 40 plates was 12.7% and 9.6%, respectively. hs-CRP was assessed by the immunoturbidimetric CRP-Latex (II) hs assay from Denka Seiken using a Hitachi 911 analyzer. The assay was performed according to the manufacturer’s protocol and has been validated against the Dade-Behring method.¹⁸ For party control, in addition to the measurement of each sample in duplicate, ~6% of samples were measured as blinded replicates on different dates to assess repeatability of measurements of Lp-PLA₂, hs-CRP, and other analytes. The reliability coefficient for blinded quality control replicates was 0.76 for the Lp-PLA₂ assay (67 blinded replicates) and 0.95 for the hs-CRP assay (70 blinded replicates).

Statistical Analyses

For the primary analysis, all variables were categorized, with cutpoints taken from the National Cholesterol Education Program Adult Treatment Panel III (ATP III) guidelines for cholesterol¹⁹ and the Joint National Committee VI guidelines for blood pressure.²⁰ Some categories were combined to maintain sufficient numbers of events per cell. Tertiles of the major study covariate, Lp-PLA₂, were used. For hs-CRP, both tertiles and American Heart Association (AHA)/Centers for Disease Control and Prevention (CDC) cutpoints²¹ were examined. Covariates also were treated as continuous to examine the potential (non)linear trend in ancillary analyses. The primary null hypothesis was that Lp-PLA₂ is not predictive of CHD events, over and above a set of traditional risk factors included in the model, with special attention to the interrelationship of Lp-PLA₂ with LDL-C and hs-CRP. The association was tested at the 0.05 level using a Wald test for the 2-sided alternative.

Crude and adjusted (for demographic factors: race, sex, age) means or proportions of baseline variables were examined in cases versus noncases using ANCOVA and logistic regression.²² Beyond basic demographic variables, variables for risk factors recommended by ATP III²² for CHD risk assessment were considered as potential confounders: LDL-C, HDL cholesterol (HDL-C), total cholesterol, diabetes, smoking, and hypertension. Weighted Pearson and Spearman’s rank correlation coefficients were computed between variables among subjects in the CRS. In all analyses, weighting schemes based on sampling proportions were used so that the resulting inferences were pertinent to the entire cohort.

For the association between Lp-PLA₂ level and incident CHD, the Cox proportional hazards model was used to investigate the independent and joint prognostic effects, accounting for the fact that all incident CHD cases are included but only a stratified random sample of the full cohort. The statistical method and computer software used were developed for case–cohort design within a framework of proportional hazard regression, with an appropriate modification to take into account the stratified nature of the CRS and robust variance estimation.²³ The results were summarized as hazard ratios (HRs) with 95% CIs. Tests for various potential interactions and (non)linearity were conducted as a secondary analysis, and subgroup analyses were considered to confirm findings. For the overall association of Lp-PLA₂ and outcome, a χ² test statistic was calculated. All other overall associations were tested similarly. SAS version 8 was used for all statistical analyses, except that SUDAAN version 8.0.0 was used to compute probability values for weighted correlation coefficients.

Results

Of the 608 CHD events, 41.6% were nonfatal myocardial infarctions, 9.5% were silent myocardial infarctions, 39.0% were revascularization procedures, and 9.9% were fatal events, with mean time to event 4.1 years. Baseline charac-
risk factors, including LDL-C and HDL-C, the relative risk associated with increased CHD risk (1.78 HR, 95% CI 1.33 to 2.39) in a model adjusted for age, sex, and race (Table 4). In a Cox proportional hazards model adjusted for age, sex, and race, high hs-CRP as defined by the AHA/CDC cutpoints was associated with a significant increase in risk (2.53 HR, 95% CI 1.88 to 3.40) (Table 3). Further adjustment for smoking, hypertension, diabetes, LDL-C, and HDL-C attenuated risk associated with high hs-CRP, but risk remained significantly elevated (1.72 HR, 95% CI 1.24 to 2.39). For individuals with LDL-C <130 mg/dL, approximately the median LDL-C in this population, high hs-CRP was associated with increased CHD risk (1.76 HR, 95% CI 1.02 to 3.03). The use of tertiles for hs-CRP and the addition of BMI to the model did not significantly alter the findings (data not shown).

Lp-PLA2 levels in the highest tertile (≥422 μg/L) were associated with increased CHD risk (1.78 HR, 95% CI 1.33 to 2.38) in a model adjusted for age, sex, and race (Table 4). In a Cox proportional hazards model also adjusted for traditional risk factors, including LDL-C and HDL-C, the relative risk

### Table 1. Weighted-Adjusted Means or Prevalences of Risk Factors at Baseline (Visit 2)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cases (n=608)</th>
<th>Noncases (n=740)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y*</td>
<td>58.5</td>
<td>56.7</td>
<td>...</td>
</tr>
<tr>
<td>Female, %*</td>
<td>32.2</td>
<td>58.9</td>
<td>...</td>
</tr>
<tr>
<td>African American, %*</td>
<td>22.9</td>
<td>25.0</td>
<td>...</td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>28.2</td>
<td>19.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>28.7</td>
<td>28.1</td>
<td>0.014</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>27.8</td>
<td>15.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension (history), %</td>
<td>51.0</td>
<td>32.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>127.5</td>
<td>121.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>73.1</td>
<td>72.6</td>
<td>0.350</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>219.7</td>
<td>207.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>144.8</td>
<td>124.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL-C, mg/dL</td>
<td>45.6</td>
<td>51.2</td>
<td></td>
</tr>
<tr>
<td>LDL-C, mg/dL</td>
<td>145.1</td>
<td>131.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lp-PLA2, μg/L</td>
<td>404</td>
<td>373</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>hs-CRP, mg/L</td>
<td>4.05</td>
<td>3.04</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Unadjusted mean or proportion; all others are age-, race-, and sex-adjusted mean or proportion.
†Median LDL-C was 145 mg/dL for cases and 129 mg/dL for noncases.
‡Adjusted for age, sex, smoking status, systolic blood pressure, LDL-C, HDL-C, and diabetes.
§n=204 cases and 369 noncases.

Compared with noncases, individuals with incident CHD had significantly higher BMI, systolic blood pressure, and levels of total cholesterol, triglycerides, and LDL-C and significantly lower HDL-C levels. Hypertension, diabetes, and current smoking were more prevalent in CHD cases. In addition to these differences in traditional risk factors, the weighted mean levels of both Lp-PLA2 and hs-CRP were significantly lower HDL-C levels. Hypertension, diabetes, and current smoking were more prevalent in CHD cases. In addition to these differences in traditional risk factors, the weighted mean levels of both Lp-PLA2 and hs-CRP were higher in cases than noncases, 404 versus 372 μg/L and 4.05 versus 3.04 mg/L, respectively.

Lp-PLA2 levels was positively correlated with LDL-C (r=0.36) and total cholesterol (r=0.23) levels and negatively correlated with HDL-C level (r=-0.33) in both men and women (Table 2). There was a weak positive correlation with triglyceride (r=0.13) and no significant correlation with hs-CRP or BMI. Spearman’s rank correlation gave similar results. Weighted mean Lp-PLA2 was 421 μg/L in men and

### Table 2. Weighted Correlation Between Lp-PLA2 and Other Risk Factors

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Pearson Correlation Coefficient</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol</td>
<td>0.23</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LDL-C</td>
<td>0.36</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HDL-C</td>
<td>-0.33</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>0.04</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>-0.01</td>
<td>NS</td>
</tr>
<tr>
<td>hs-CRP</td>
<td>-0.05</td>
<td>NS</td>
</tr>
<tr>
<td>BMI</td>
<td>-0.02</td>
<td>NS</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>0.13</td>
<td>0.0006</td>
</tr>
</tbody>
</table>

NS indicates nonsignificant (P≥0.05)

**Table 3. CHD HRs (95% CI) by hs-CRP Categories Defined by AHA/CDC**

<table>
<thead>
<tr>
<th>hs-CRP Categories*</th>
<th>Average Risk (1.0–3.0 mg/L)</th>
<th>High Risk (&gt;3.0 mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1†</td>
<td>1.61 (1.21–2.16)</td>
<td>2.53 (1.88–3.40)</td>
</tr>
<tr>
<td>Model 2†</td>
<td>1.31 (0.96–1.80)</td>
<td>1.72 (1.24–2.39)</td>
</tr>
<tr>
<td>Model 2, LDL-C &lt;130 mg/dL§</td>
<td>1.18 (0.71–1.96)</td>
<td>1.76 (1.02–3.03)</td>
</tr>
</tbody>
</table>

*Low risk (<1 mg/L) is reference; ARIC tertiles were <1.01, 1.01–2.82, and >2.82 mg/L.
†Adjusted for age, sex, and race.
‡Adjusted for age, sex, race, smoking status, systolic blood pressure, LDL-C, HDL-C, and diabetes.
§n=204 cases and 369 noncases.

339 μg/L in women, 366 μg/L in individuals <55 years old and 384 μg/L in individuals ≥55 years old, 388 μg/L in whites and 333 μg/L in African Americans, 362 μg/L in diabetics and 376 μg/L in nondiabetics, and 404 μg/L in current smokers and 366 μg/L in nonsmokers.

Because hs-CRP tertiles in ARIC (<1.01, 1.01 to 2.82, and >2.82 mg/L) were similar to the cutpoints defined in the AHA/CDC guidelines (<1 mg/L, 1 to 3 mg/L, >3 mg/L), the AHA/CDC cutpoints were used to facilitate comparison across studies. In a Cox proportional hazards model adjusted for age, sex, and race, high hs-CRP as defined by the AHA/CDC cutpoint of >3.0 mg/L was associated with a significant increase in risk (2.53 HR, 95% CI 1.88 to 3.40) (Table 3). Further adjustment for smoking, hypertension, diabetes, LDL-C, and HDL-C attenuated risk associated with high hs-CRP, but risk remained significantly elevated (1.72 HR, 95% CI 1.24 to 2.39). For individuals with LDL-C <130 mg/dL, approximately the median LDL-C in this population, high hs-CRP was associated with increased CHD risk (1.76 HR, 95% CI 1.02 to 3.03). The use of tertiles for hs-CRP and the addition of BMI to the model did not significantly alter the findings (data not shown).

Lp-PLA2 levels in the highest tertile (≥422 μg/L) were associated with increased CHD risk (1.78 HR, 95% CI 1.33 to 2.38) in a model adjusted for age, sex, and race (Table 4). In a Cox proportional hazards model also adjusted for traditional risk factors, including LDL-C and HDL-C, the relative risk

### Table 4. CHD HRs (95% CI) by Lp-PLA2 Tertiles

<table>
<thead>
<tr>
<th>Lp-PLA2 Tertiles*</th>
<th>2 (310–422 μg/L)</th>
<th>3 (≥422 μg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1†</td>
<td>1.26 (0.94–1.69)</td>
<td>1.78 (1.33–2.38)</td>
</tr>
<tr>
<td>Model 2†</td>
<td>1.02 (0.73–1.43)</td>
<td>1.16 (0.82–1.65)</td>
</tr>
<tr>
<td>Model 2, LDL-C &lt;130 mg/dL§</td>
<td>1.83 (1.11–3.00)</td>
<td>1.99 (1.17–3.38)</td>
</tr>
<tr>
<td>Model 3§</td>
<td>1.00 (0.71–1.41)</td>
<td>1.15 (0.81–1.63)</td>
</tr>
<tr>
<td>Model 3, LDL-C &lt;130 mg/dL§</td>
<td>1.83 (1.10–3.05)</td>
<td>2.08 (1.30–3.62)</td>
</tr>
</tbody>
</table>

*Lowest tertile (<310 μg/L) is reference.
†Adjusted for age, sex, and race.
‡Adjusted for age, sex, race, smoking status, systolic blood pressure, LDL-C, HDL-C, and diabetes.
§Adjusted for age, sex, race, smoking status, systolic blood pressure, LDL-C, HDL-C, diabetes, and hs-CRP.
Association of Lp-PLA$_2$ and hs-CRP with incident CHD in patients with low LDL-C (<130 mg/dL). CHD risk in individuals with elevations in both Lp-PLA$_2$ (highest tertile) and hs-CRP (high-risk category as defined in the AHA/CDC guidelines) was 3 times greater than in individuals with low to medium levels (first and second tertiles) of Lp-PLA$_2$ and hs-CRP.

Discussion

In the ARIC study, Lp-PLA$_2$ and hs-CRP levels were higher in middle-aged American men and women who subsequently developed CHD events than in those who remained free of CHD.

Two previous studies have examined Lp-PLA$_2$ and hs-CRP levels in cases with incident CHD and controls, and both studies found positive associations of Lp-PLA$_2$ and hs-CRP with CHD risk.\cite{10,11} In ARIC, both Lp-PLA$_2$ and hs-CRP were associated with incident CHD after adjustment for age, sex, and race, with 1.78 HR (95% CI 1.33 to 2.38) for the highest Lp-PLA$_2$ tertile ($\geq 422$ mg/L) and 2.53 HR (95% CI 1.88 to 3.40) for hs-CRP $>3.0$ mg/L. The HRs for high Lp-PLA$_2$ in this study are similar to those reported in WOSCOPS\cite{10} and the Women’s Health Study\cite{11} in the unadjusted models. Although all 3 studies found that Lp-PLA$_2$ levels were increased in individuals with subsequent CHD events, results varied among the studies when statistical models examined whether Lp-PLA$_2$ level had additional predictivity beyond traditional risk factors. In WOSCOPS, Lp-PLA$_2$ remained a significant predictor after adjustment for traditional risk factors and inflammatory factors, including hs-CRP.\cite{10} However, in the Women’s Health Study, the predictivity of Lp-PLA$_2$ was no longer statistically significant after adjustment for cardiovascular risk factors.\cite{11} In the ARIC study, the relation between Lp-PLA$_2$ and CHD risk was attenuated after adjustment for traditional risk factors including LDL-C and HDL-C, but further analysis motivated by the significant interactions among Lp-PLA$_2$, hs-CRP, and LDL-C indicated that the association remained significant, independent of other traditional risk factors but modifiable by hs-CRP in individuals with low LDL-C (<130 mg/dL). We did not find any significant, meaningful nonlinearity of Lp-PLA$_2$ using polynomial and spline regression, but complex nonlinearity remains a possibility. Moreover, the significant 3-way interaction ($P=0.02$ in a model with categorical variables and $P=0.001$ in a model with continuous variables) needs more statistical investigation in future research in this and other populations. The differing results among these studies may be attributed to the markedly different populations. WOSCOPS enrolled middle-aged hypercholesterolemic men in Scotland, with LDL-C entry criterion within a narrow range of 174 to 232 mg/dL, high prevalence of other risk factors, and 5-year event rate of 7.9% in the placebo group (1.6%/yr).\cite{24} In addition, half the patients in WOSCOPS were assigned to pravastatin therapy, which lowered LDL-C by 26% on average. The Women’s Health Study examined middle-aged American women who were mostly professionals and had a lower event rate (1.4% over 6.2 years, or 0.2%/yr),\cite{11} enrolled fewer African Americans (2.3%) and fewer diabetic patients (2.6%)\cite{23} than ARIC, and included only 123 cases (49 of which were stroke) and 123 controls in the Lp-PLA$_2$ analysis.\cite{11} In contrast, participants in ARIC were both men and women, including a substantial number of African Americans, and had a wide range of LDL-C levels, as would be expected in the US population; in this analysis of ARIC, the 10th percentile for LDL-C was 89 mg/dL and the 90th percentile was 179 mg/dL, and the event rate was 6.1% over 7 years, or 0.9%/yr.

For the hs-CRP analysis, the cutpoints defined in the AHA/CDC guidelines (1 and 3 mg/L)\cite{3} were used because they were similar to the tertile cutpoints in ARIC (1.01 and 2.82 mg/L). A previous analysis that examined hs-CRP in a different ARIC cohort showed similar risk for the upper 2 quintiles.\cite{25} The AHA/CDC guidelines provide for the assessment of hs-CRP in individuals at intermediate CHD risk (10% to 20% 10-year risk) as an adjunct to major risk factors to refine risk assessment and in considering whether to...
intensify therapy. There is a consensus that individuals with
CHD risk >20% need preventive intervention and therefore CRP measurement will not influence therapy. Screening
very-low-risk populations is not recommended and not thought to be cost-effective, although some groups have
considered intermediate risk to include 6% to 20%.27
The ATP III guidelines recommend that calculated 10-year
risk for a CHD event be used to determine which patients
should receive lipid-lowering therapy and the target level for
LDL-C. Two large placebo-controlled randomized clinical
trials of statins in high-risk patients have shown that patients
benefited from therapy regardless of baseline LDL-C.28,29 In
the current guidelines, for individuals with LDL-C <130
mg/dL, drug therapy is not recommended in primary preven-
tion and is considered optional for individuals with CHD or
equivalent (ie, 10-year risk estimate >20%).30 If high-risk
patients with LDL-C <130 mg/dL receive significant benefit
from lipid-lowering drug therapy, as suggested by recent
clinical trials, future guidelines may focus more on novel
ways to assess CHD risk in low–LDL-C patients to determine
who should be selected. This is an important population for
CHD prevention, because approximately one third of all
events (204 cases in ARIC) occurred in persons with LDL-C
<130 mg/dL.

A post hoc analysis of the Air Force/Texas Coronary
Atherosclerosis Prevention Study (AFCAPS/TexCAPS) sug-
gested that measuring hs-CRP may be useful for targeting
statin therapy in primary prevention of acute coronary
events.31 AFCAPS/TexCAPS enrolled middle-aged men and
women with average LDL-C and low HDL-C levels, and for
individuals with LDL-C below the median (149.1 mg/dL),
only those with elevated hs-CRP had reduced risk with
lovastatin therapy.

The results from ARIC support the rationale that Lp-PLA2
and hs-CRP may be useful to identify patients at increased
CHD risk who have low LDL-C (<130 mg/dL) and are not
targeted for drug therapy by the current guidelines. ARIC had
only a single measurement of Lp-PLA2 and hs-CRP; associ-
atations might have been stronger with multiple measurements
of these biomarkers. In addition, the risk for Lp-PLA2 may
have been underestimated because of a lower reliability
efficiency coefficient for the Lp-PLA2 manual ELISA than for the
hs-CRP automated immunonoturbidimetric assay (0.76 versus
0.95). A large prospective randomized trial will test the
hypothesis that hs-CRP measurement can identify high-risk
patients with LDL-C <130 mg/dL and no clinical evidence of
CHD who may benefit from statin therapy.32

Although our results support the use of novel blood tests to
identify high-risk patients who may benefit from primary
prevention, they are also consistent with a putative causal role
for both Lp-PLA2 and hs-CRP in atherogenesis and CHD
events. Lp-PLA2 is bound primarily with LDL, with an
increased concentration in small, dense LDL.33 Small LDL has
enhanced penetration into the vessel wall34 and enhanced
susceptibility to oxidation.35 Lp-PLA2 is the enzyme
responsible for the hydrolysis of oxidized phospholipids and the
generation of lysophosphatidylcholine, which can lead to
increased expression of adhesion molecules. Thus, increased
Lp-PLA2 in LDL may enhance the atherogenicity of LDL by
increasing vascular inflammation. High levels of hs-CRP,
which is an acute-phase reactant, may also provoke vascular
inflammation,33 and hs-CRP may preferentially bind to oxi-
dized LDL.34 Individuals with low LDL-C but high Lp-PLA2
and hs-CRP may therefore have much greater atherogenicity
from LDL than would be expected by the absolute level of
LDL-C. Statins lower LDL-C level and LDL particle number,
reduce hs-CRP level,7 and reduce Lp-PLA2 activity.35 How-
ever, many patients continue to have elevated hs-CRP and
Lp-PLA2 even on statin therapy (Chris J. Packard, DSc,
personal communication, 2003). Other therapies, such as
weight loss and high-dose aspirin, also reduce hs-CRP levels.
Fibrates have been shown to reduce Lp-PLA2 activity,36 and
a novel agent that inhibits Lp-PLA2 is currently in phase II
development.37 Therefore, in addition to potentially identify-
ing high-risk but currently untreated patients who may benefit
from therapies such as statins to reduce CHD events, mea-
surement of Lp-PLA2 and hs-CRP may be useful to identify
cohorts of patients for clinical trials to determine whether
inhibition of Lp-PLA2, or reduction/inhibition of hs-CRP
reduces CHD events. In summary, both Lp-PLA2 and hs-CRP
may be complementary in identifying middle-aged individu-
als with high CHD risk but low LDL-C.

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