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# Coronary Heart Disease Prediction From Lipoprotein Cholesterol Levels, Triglycerides, Lipoprotein(a), Apolipoproteins A-I and B, and HDL Density Subfractions The Atherosclerosis Risk in Communities (ARIC) Study

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**Background**—Despite consensus on the need for blood cholesterol reductions to prevent coronary heart disease (CHD), available evidence on optimal cholesterol levels or the added predictive value of additional lipids is sparse.

**Methods and Results**—After 10 years follow-up of 12 339 middle-aged participants free of CHD in the Atherosclerosis Risk in Communities Study (ARIC), 725 CHD events occurred. The lowest incidence was observed in those at the lowest LDL cholesterol (LDL-C) quintile, with medians of 88 mg/dL in women and 95 mg/dL in men, and risk accelerated at higher levels, with relative risks (RRs) for the highest quintile of 2.7 in women and 2.5 in men. LDL-C, HDL-C, lipoprotein(a) [Lp(a)], and in women but not men, triglycerides (TG) were all independent CHD predictors, providing an RR, together with blood pressure, smoking, and diabetes, of 13.5 in women and 4.9 in men. Lp(a) was less significant in blacks than whites. Prediction was not enhanced by HDL-C density subfractions or apolipoproteins (apo) A-I or B. Despite strong univariate associations, apoB did not contribute to risk prediction in subgroups with elevated TG, with lower LDL-C, or with high apoB relative to LDL-C.

**Conclusions**—Optimal LDL-C values are <100 mg/dL in both women and men. LDL-C, HDL-C, TG, and Lp(a), without additional apolipoproteins or lipid subfractions, provide substantial CHD prediction, with much higher RR in women than men. (*Circulation*. 2001;104:1108-1113.)

**Key Words:** lipoproteins ■ apolipoproteins ■ coronary disease ■ follow-up studies

Recently reported clinical trials have provided strong support for currently accepted recommendations for drug treatment and lifestyle modifications for lowering lipid levels to prevent coronary heart disease (CHD).<sup>1-3</sup> Additional evidence from large prospective studies, however, can help both to define optimal lipid levels in women and men and to determine whether CHD risk can be assessed adequately from total cholesterol or LDL cholesterol (LDL-C), HDL-C, and triglycerides (TG) or whether additional prediction is gained from measuring lipoprotein (a) [Lp(a)], apolipoproteins A-I and B (apoA-I, apoB), or HDL density subfractions. We investigated these questions using information from 10 years of follow-up of 12 339 Atherosclerosis Risk in Communities (ARIC) participants.

## Methods

### Study Population

Between 1987 and 1989, ARIC examined population-based samples of residents 45 to 64 years old from 4 communities in North

Carolina, Mississippi, Minnesota, and Maryland. Eligible participants had no evidence of CHD at baseline (ECG evidence or history of myocardial infarction, angina, coronary bypass, or angioplasty), were taking no lipid-lowering medications, and had fasting TG levels <400 mg/dL. Of 15 792 examined, 11% had prevalent CHD, 3% took lipid medications, and 1% had elevated TG. Of the eligible participants, 743 were excluded for lack of fasting blood sample and 465 because of missing data, and 12 339 remained for analysis.

### Incident CHD

Incident CHD events included CHD death, myocardial infarction, silent infarction by ECG, coronary bypass, and angioplasty occurring before January 1998. Deaths and hospitalization events were ascertained by annual follow-up calls and vital record and community hospital surveillance. CHD death was defined as lacking a probable non-CHD cause with either a recent myocardial infarction, chest pain within 72 hours of death, or a history of CHD. A more complete description of event ascertainment has been published.<sup>4</sup>

### Baseline Measurements

The 12-hour fasting plasma lipid assays and their performance have been described.<sup>5</sup> Cholesterol and TG were measured enzymatically.

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**TABLE 1. Age- and Race-Adjusted Means (SD) for Lipid Factors for ARIC Women and Men With and Without Incident CHD**

	Women		Men	
	CHD	No CHD	CHD	No CHD
No. of subjects	216	6691	509	4923
Total cholesterol, mmol/L	5.96 (1.07)	5.59 (1.07)	5.72 (1.01)	5.40 (1.00)
LDL-C, mmol/L	3.89 (1.03)	3.48 (1.02)	3.91 (0.94)	3.56 (0.94)
HDL-C, mmol/L	1.30 (0.44)	1.51 (0.44)	1.07 (0.35)	1.18 (0.35)
TG, mmol/L	1.68 (0.66)	1.30 (0.66)	1.63 (0.74)	1.44 (0.73)
Lp(a), $\mu$ g/mL	128.1 (104.2)	106.7 (103.8)	103.4 (91.1)	87.4 (90.9)
ApoB, g/L	1.01 (0.28)	0.90 (0.28)	1.03 (0.27)	0.94 (0.27)
ApoA-1, g/L	1.33 (0.32)	1.44 (0.32)	1.17 (0.26)	1.23 (0.26)
HDL <sub>2</sub> -C, mmol/L	0.36 (0.24)	0.45 (0.24)	0.26 (0.17)	0.29 (0.17)
HDL <sub>3</sub> -C, mmol/L	0.94 (0.27)	1.06 (0.27)	0.81 (0.26)	0.89 (0.26)

All CHD vs No CHD comparisons are statistically significant at  $P < 0.005$ .

Cholesterol was measured in total HDL and HDL<sub>3</sub> separated by the method of Warnick et al.<sup>6</sup> LDL-C was calculated. For examination 1, apoA-I and apoB were determined by a radioimmunoassay shown to be accurate and reliable done in frozen plasma.<sup>7,8</sup> LDL standard and tracer were prepared by zonal ultracentrifugation.<sup>8</sup> ApoB levels are well preserved by use of our sample processing methods but are reduced 7% by freezing.<sup>9</sup> Examination 2 apoA-I and apoB assays were based on immunoturbidimetry. Lp(a) was measured as total protein [apo(a) plus apoB], which represents  $\approx 30\%$  of total Lp(a) lipoprotein mass, with a double-antibody ELISA for apo(a).<sup>10</sup> Aliquots from 7% of all samples were stored an additional week. Analysis of these "blind" duplicates provides a measure of variability that includes processing, storage, and shipping effects. Blind duplicate coefficients of variation for total cholesterol, LDL-C, TG, HDL-C, HDL<sub>3</sub>-C, apoB, and apoA-I were 5%, 10%, 7%, 5%, 12%, 16%, and 14%, respectively. For the immunoturbidimetric assays, they were 17% for apoB and 12% for apoA-I. Reliability estimates, based on an intraindividual variability study with 3 measurements at 1- to 2-week intervals, although lower for apoA-I (0.60) and HDL<sub>3</sub>-C (0.70) than for total cholesterol (0.94), LDL-C (0.91), TG (0.85), and HDL-C (0.94), were generally greater than other published values.<sup>11</sup>

## Data Analysis

Analyses were performed separately by sex. Mean lipid values were calculated for participants with and without incident CHD after age and race adjustment. Relative risks (RRs) were calculated for lipid quintiles considering 1 lipid at a time, adjusted for age and race, by Cox proportional hazards regression. Risks related to lipids in an approximately log-linear fashion. There were no significant race-lipid interactions except among women for HDL<sub>2</sub>-C ( $P = 0.02$ ). Tests showed proportionality over time for all lipids and for race and age.

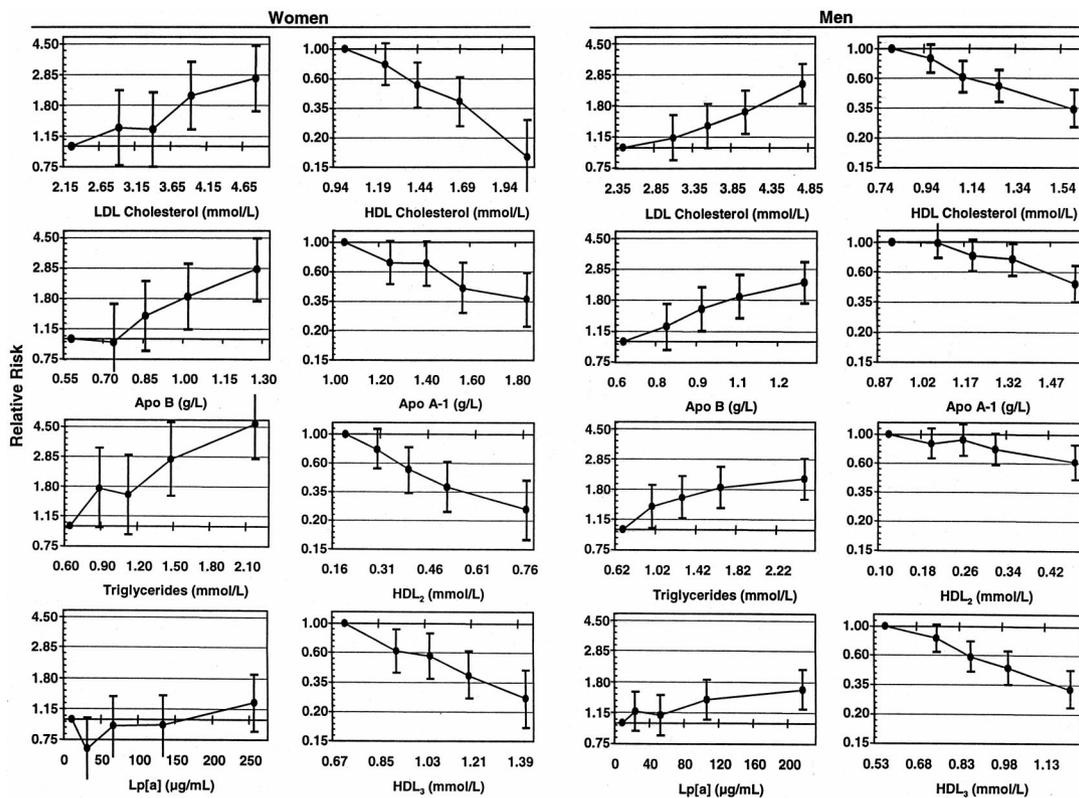
Multivariable proportional hazards analysis was used to assess the predictive value of adding Lp(a), apolipoproteins, or HDL subfractions to models including LDL-C, HDL-C, and TG. RR associated with approximate SD increases of each lipid factor were calculated with adjustment for both age and race and after nonlipid risk factors had been added. Participants were ranked by their CHD risk as calculated by these models and grouped into risk deciles. Model RRs were then calculated as the event rate among persons in the 2 deciles of highest risk divided by the CHD rate in the lowest 4 deciles, with confidence intervals estimated by bootstrap replication.<sup>12</sup> To determine the relative strength of associations for lipoproteins versus apolipoproteins while reducing their intraindividual variation differences, analyses were repeated using the mean of examination-1 and examination-2 values for LDL-C, apoB, HDL-C, apoA-I, and TG.

## Results

Over 10 years of follow-up, 216 incident CHD events occurred in women and 509 in men (Table 1). Age- and

race-adjusted baseline levels of cholesterol, LDL-C, TG, apoB, and Lp(a) were higher and HDL-C, apoA-I, HDL<sub>2</sub>-C, and HDL<sub>3</sub>-C were lower in women and men with subsequent CHD than in comparison subjects ( $P < 0.005$  for all 18 comparisons). Figure 1 shows the adjusted RR for upper lipid quintiles relative to the lowest quintile, with each quintile plotted at its median lipid value. No threshold for the association of any lipid with CHD was apparent for either sex. For example, the lowest risk was found in the lowest LDL-C quintile, with median values of 2.27 mmol/L (88 mg/dL) in women and 2.45 mmol/L (95 mg/dL) in men, and risks accelerated with increasing values. LDL-C and apoB were associated with similar top-quintile RRs: 2.7 and 2.8, respectively, in women and 2.5 and 2.4, respectively, in men. HDL-C, however, was associated with greater CHD protection than apoA-I, with top quintile RRs of 0.16 and 0.38, respectively, in women, and 0.36 and 0.50, respectively, in men. TGs were associated with much greater top quintile RRs in women (4.7) than men (2.1).

An  $\approx 1$ -SD (1 mmol/L) LDL-C increase was associated with age- and race-adjusted RRs of 1.37 in women and 1.42 in men. RRs were similar for total cholesterol, namely, 1.32 in women and 1.34 in men for a 1-SD increase (1.05 mmol/L). Table 2 presents RR in models including several lipids together. Four models are calculated, first adjusting for age and race and then additional covariates. Model 1 includes LDL-C, HDL-C, and TG. Model 2 adds Lp(a) to model 1, and model 3 adds apolipoproteins to model 1. Model 4 includes LDL-C, TG, and HDL-C density subfractions. For women, the age- and race-adjusted model 1 shows all lipids to be independently significant, with RRs per SD increase of 1.23 for LDL-C, 0.69 for HDL-C, and 1.29 for TG. Lp(a) was also independently significant, with an RR of 1.17 (model 2). In model 3, neither apoB nor apoA-I was independently significant, and their RRs were each close to 1.0. In model 4, RRs were 0.87 for HDL<sub>2</sub>-C and 0.76 for HDL<sub>3</sub>-C, but only the latter was significant. Overall prediction was similar for the 4 models, with model RRs ranging only from 6.94 to 7.00, not significantly different from each other. Findings were similar in men. Model 1 showed strong independent RRs for LDL-C



**Figure 1.** RR of CHD for sex-specific lipid factor quintiles with adjustment for age and race in ARIC women and men.

(1.40) and HDL-C (0.64), but only 1.07 for TG (not significant). As for women, Lp(a) was independently significant (RR=1.15, model 2), and apolipoproteins had nonsignificant RRs close to 1.0 (model 3). RRs were 0.95 for HDL<sub>2</sub>-C and 0.70 for HDL<sub>3</sub>-C (model 4), and only the latter was significant. Model RRs again showed a narrow range, from 3.68 to 4.09, not significantly different from each other.

Figures 2, 3, and 4 plot the number of incident CHD events that occurred in each decile of risk predicted from different models. Figure 2 shows better prediction for model 1, which includes age, race, LDL-C, HDL-C, and TG, than for a model that includes only age, race, and LDL-C, with more CHD events in the upper deciles of risk and fewer events in the lower deciles. Figure 3 shows that, despite the independent statistical significance of Lp(a), model 2 with Lp(a) provided only a slight overall gain in prediction compared with model 1, apparent primarily in the highest risk decile. Figure 4, however, confirms the lack of independent significance of the apolipoproteins by the near congruence of the curves for models 3 and 1. In all models, women had very few events in low-risk deciles.

The “fully adjusted” models, including smoking, blood pressure, antihypertensive medication use, and diabetes, showed similar patterns (Table 2). As before, when added to models including LDL-C, HDL-C, and TG, Lp(a) was a significant independent CHD predictor and apolipoproteins were not. Model RRs were higher with the added nonlipid covariates, and their range across models remained narrow, 11.81 to 13.48 for women and 4.82 to 4.92 for men. The models again show much better prediction in women than men.

Additional analyses were undertaken to discover why apoB showed no independent association with CHD. When apoB or LDL-C was considered alone, age- and race-adjusted RRs per approximate SD were 1.32 in women and 1.31 in men for apoB, nearly as large as the 1.37 in women and 1.42 in men for LDL-C. In 3-lipid models, however, TG and LDL-C were significant, but apoB became nonsignificant, with RRs of 0.97 in women and 1.05 in men. Model 3 was repeated in 2 subgroups in which apoB might be more predictive: persons with LDL-C <160 mg/dL and those with above-median TG values. In both subgroups, RR for apoB remained at or slightly below 1.0 in both sexes.

Elevated apoB might also be predictive in individuals with apoB-enriched LDL particles.<sup>13</sup> We calculated excess apoB compared with LDL-C as the observed apoB value minus that expected from linear regression of apoB on LDL-C. The 10% of men with the highest apoB excess had mean apoB values 0.38 g/L higher than expected from their LDL-C concentration. As expected, 16% were diabetic, and they had higher TG and lower HDL-C than other men. Adjusted for diabetes and other risk factors, however, CHD risk was not elevated for the top apoB decile in either sex.

Because apolipoprotein levels are less reliably estimated with the methods used than lipoprotein cholesterols, as our blind-duplicate data showed, we reasoned that their predictive ability might be enhanced by averaging. Among the 10 126 CHD-free participants with lipids measured at examinations 1 and 2, 454 post-examination 2 CHD events occurred. Despite use of average values, apoB remained statistically insignificant in the LDL-C, HDL-C, and TG models, with RRs of 0.96 in women and 1.08 in men.

**TABLE 2. RR Estimated From Multivariable Models\* Associated With SD Increases in Lipid Factors in ARIC Women and Men**

	Model No.							
	Age, Race Adjusted*				Fully Adjusted*			
	1	2	3	4	1	2	3	4
<b>Women</b>								
LDL-C (1.00 mmol/L)	1.23†	1.19†	1.27†	1.24†	1.24†	1.20†	1.32†	1.25†
HDL-C (0.40 mmol/L)	0.69†	0.68†	0.64†		0.76†	0.76†	0.72†	
TG (0.70 mmol/L)	1.29†	1.31†	1.29†	1.29†	1.14	1.15‡	1.16	1.13
Lp(a) (100 µg/mL)		1.17†				1.17†		
ApoB (0.25 g/L)			0.96				0.91	
ApoA-1 (0.30 g/L)			1.07				1.07	
HDL <sub>2</sub> -C (0.20 mmol/L)				0.87				0.93
HDL <sub>3</sub> -C (0.25 mmol/L)				0.76†				0.81†
Model RR§	6.94	7.00	6.97	7.00	11.81	13.48	11.81	12.40
90% CI model RR	4.7, 9.5	4.7, 9.5	4.7, 9.2	4.8, 9.7	7.7, 16.0	9.1, 20.3	7.0, 14.7	8.1, 18.4
<b>Men</b>								
LDL-C (1.00 mmol/L)	1.40†	1.36†	1.37†	1.43†	1.41†	1.37†	1.39†	1.44†
HDL-C (0.40 mmol/L)	0.64†	0.63†	0.66†		0.66†	0.66†	0.68†	
TG (0.70 mmol/L)	1.07	1.08	1.06	1.06	1.01	1.02	1.01	1.01
Lp(a) (100 µg/mL)		1.15†				1.15†		
ApoB (0.25 g/L)			1.03				1.02	
ApoA-1 (0.30 g/L)			0.97				0.96	
HDL <sub>2</sub> -C (0.20 mmol/L)				0.95				0.95
HDL <sub>3</sub> -C (0.25 mmol/L)				0.70†				0.72†
Model RR§	3.80	4.09	3.68	3.72	4.87	4.92	4.91	4.82
90% CI model RR	3.1, 4.6	3.3, 5.0	2.9, 4.3	3.0, 4.4	3.9, 5.8	3.9, 5.7	3.9, 5.9	3.6, 5.5

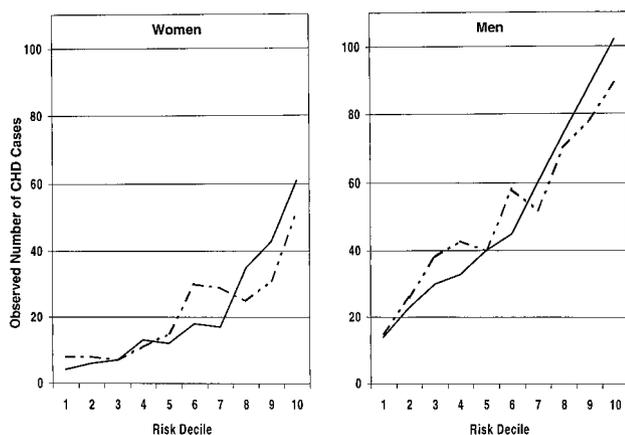
\*Proportional hazards models including LDL-C, HDL-C, and TG (model 1), model 1 plus Lp(a) (model 2), model 1 plus apoB and apoA-I (model 3), or LDL-C, TG, HDL<sub>2</sub>-C, and HDL<sub>3</sub>-C (model 4). Each model adjusted only for age and race or fully adjusted (ie, for age, race, current smoking, systolic blood pressure [mm Hg], use of medications for hypertension, and diabetes).

†*P*<0.01, ‡*P*<0.05.

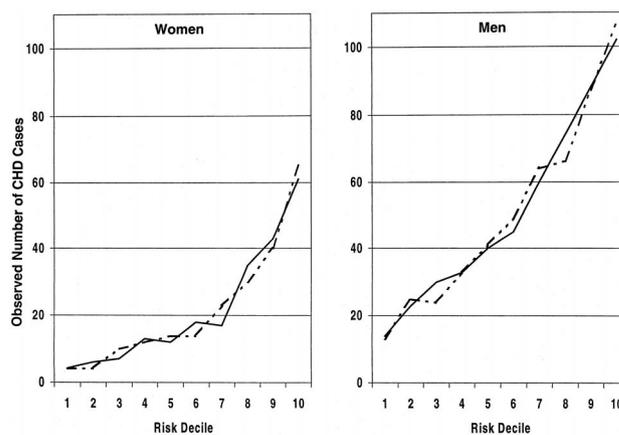
§Model RR is calculated as the CHD rate observed among persons classified in the 2 deciles of highest risk divided by the CHD rate observed in the lowest 4 deciles of risk.

Because they have much higher Lp(a) values, Lp(a) associations were examined separately in blacks. Baseline age-adjusted mean Lp(a) values were higher in participants with subsequent CHD than control subjects in all race-sex groups,

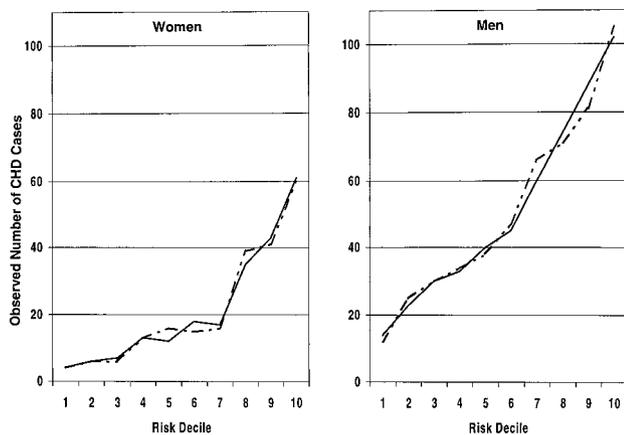
the difference being significant in white women (103 µg/mL in participants with CHD events versus 84 µg/mL in control subjects *P*=0.02) and white men (89 versus 70 µg/mL, *P*<0.001), nearly significant in black women (192 versus 164



**Figure 2.** CHD events per decile of risk: LDL-C model (including age, race, and LDL-C; dashed line) vs model 1 (including age, race, LDL-C, HDL-C, and triglycerides; solid line).



**Figure 3.** CHD events per decile of risk: model 1 (including age, race, LDL-C, HDL-C, and triglycerides; solid line) vs model 2 [including model 1 plus Lp(a); dashed line].



**Figure 4.** CHD events per decile of risk: model 1 (including age, race, LDL-C, HDL-C, and triglycerides; solid line) vs model 3 (including model 1 plus apolipoproteins A-I and B; dashed line).

$\mu\text{g/mL}$ ,  $P=0.07$ ), but not significant in black men (150 versus 145  $\mu\text{g/mL}$ ). In a model that included age, LDL-C, HDL-C, TG, and Lp(a), the coefficient for a 1-SD higher Lp(a) was 1.19 ( $P<0.05$ ) in white women, 1.20 ( $P<0.01$ ) in white men, 1.14 in black women ( $P>0.05$ ), and 1.01 in black men ( $P>0.05$ ). The number of CHD events in blacks (68 in women and 90 in men), however, was small for reliable estimation.

### Discussion

The ARIC Study, with 10-year follow-up and 725 CHD events, shows strong associations of total cholesterol, LDL-C, and TG with increased CHD risk and of HDL-C with decreased risk. No thresholds are seen for these lipids, as reported in other studies large enough to examine dose-response curves.<sup>14,15</sup> For example, for both sexes, risk of CHD death is lowest for LDL-C values of  $<100$  mg/dL, in accord with findings for total cholesterol among 325 000 men screened for the MRFIT trial.<sup>15</sup> Recent evidence from primary prevention trials in predominantly male populations shows that CHD incidence can be reduced 31% to 37% by 25% LDL-C reductions from levels of 4 to 5 mmol/L.<sup>2,3</sup> Our findings suggest that both women and men would benefit by achieving even lower LDL-C levels, although diet and other lifestyle modifications will take precedence over drug treatment in lower-risk individuals.<sup>1</sup> ARIC results indicate that CHD risk is elevated  $\approx 40\%$  for every mmol/L increment in LDL-C (1 mmol/L is 26% of the LDL-C mean of 3.9 mmol/L in ARIC), similar to the primary prevention trial results.

HDL-C associations are also continuous and strong, and the associations, like LDL-C, were independent of other lipids, as reported elsewhere.<sup>16,17</sup> Consistent with a recent review,<sup>18</sup> TG was associated with substantially greater RR in women (4.7) than men (2.1), and in women but not men, the TG association persisted in analyses that included LDL-C, HDL-C, and Lp(a).

Lp(a) was associated with modest RRs, which, because of low correlations with other risk factors,<sup>19</sup> were independent in both sexes. A recent meta-analysis of prospective studies showed top tertile Lp(a) values to be associated with a CHD RR of 1.7 in men<sup>19</sup> but, with fewer available data, to be not significant in

women.<sup>20,21</sup> Despite independent statistical significance in ARIC, the clinical utility of Lp(a) measurement must be judged against its cost of measurement, the present lack of a direct therapeutic option, and the very small gain in overall prediction from adding Lp(a) to other lipids (Table 2, Figure 3). ARIC results suggest that despite higher values, Lp(a) may confer less risk in blacks than whites. An earlier ARIC report showed Lp(a) to be less consistently associated with carotid atherosclerosis in blacks than whites.<sup>22</sup>

ApoA-I and apoB, strongly predictive of CHD when considered alone, did not contribute at all when considered together with LDL-C, HDL-C, and TG. The lack of independent prediction from apoA-I is in accord with a review by Rader et al<sup>23</sup> and more recent prospective studies.<sup>16,24</sup> Prospective studies do not, however, give consistent results with respect to apoB. In 2 studies reviewed,<sup>23</sup> apoB predicted CHD better than total cholesterol, but in 2 others it did not. Since then, apoB and total cholesterol were found to predict CHD with similar RR in one study,<sup>24</sup> but LDL-C was a stronger predictor in the much larger GRIPS study.<sup>16</sup>

The lack of independent CHD prediction by the apolipoproteins may result from their greater variability. When we studied CHD incidence in relation to the average of 2 measurements 3 years apart, however, the apolipoproteins did not gain in predictive value. We also found that apoB lacked independent prediction in persons without elevated LDL-C or those with elevated TG. An earlier ARIC publication showed that apoB was not an independent CHD predictor among diabetics.<sup>25</sup> We also found no significant risk in persons who might have a "hyperapoB" syndrome.<sup>13,26</sup> There is little doubt that small LDL, marked by high apoB relative to LDL-C, is associated with CHD.<sup>27,28</sup> Small LDL, however, is associated with elevated TG, particularly postprandial TG, via cholesteryl ester transfer protein-mediated transfer and subsequent hepatic lipase action on TG-rich LDL. Thus, it is not surprising that LDL size often does not predict CHD independently of HDL-C and TG<sup>27</sup> or that ARIC results show that TG eliminates the independent predictive value of apoB.

Despite the large size of ARIC, estimates of multivariate independent associations can be imprecise if the variables are strongly intercorrelated. With correlations of apoB with LDL-C and apoA-I with HDL-C ranging from 0.7 to 0.8,<sup>5</sup> we might have failed to find weak CHD associations. The same strong LDL-C and HDL-C associations and lack of independent associations for apoA-I and apoB, however, were found in relation to carotid atherosclerosis measured in the entire ARIC population by ultrasound imaging.<sup>5</sup>

This study indicates strong CHD prediction based on LDL-C, HDL-C, TG, and Lp(a), with RRs of 4.9 in men and 13.5 in women when nonlipid risk factors are included. The much higher RR in women than men, largely because of the infrequency of CHD events in women who lacked risk factor elevations, is striking and suggests the value of further risk assessment research in middle-aged men.

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