

Lipoprotein(a), Measured With an Assay Independent of Apolipoprotein(a) Isoform Size, and Risk of Future Cardiovascular Events Among Initially Healthy Women

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LIPOPROTEIN(A), A LIPOPROTEIN described more than 40 years ago,¹ is a specific class of lipoprotein particles found in human plasma, made up of a single copy of apolipoprotein B-100 linked to an apolipoprotein(a) component. It differs from low-density lipoprotein cholesterol (LDL-C) by this apolipoprotein(a) component, a protein with marked size heterogeneity.² Its structural homology to plasminogen³ may lead to inhibition of fibrinolysis, contributing to a thrombogenic milieu.^{4,5} High lipoprotein(a) levels correlate with a greater degree of atherosclerotic coronary artery disease⁶ and carotid wall thickening^{7,8} but not with coronary calcium.⁹ Lipoprotein(a) may induce chemotaxis of monocytes and affect plasminogen activator inhibitor 1 and tissue factor expression.^{10,11} Plasma levels are stable over time and more than 90% of the variation in plasma lipoprotein concentrations may be attributable to the apolipoprotein(a) gene.^{12,13}

Epidemiological studies of lipoprotein(a) have shown disparate results, leading to controversy about the clinical utility of routinely measuring lipoprotein(a). Although many studies have shown positive associations,¹⁴⁻²⁰ others have shown weak²¹ or no associations.^{9,22-26} Part of this controversy has

Context Controversy exists as to whether lipoprotein(a), a lipoprotein with homology to plasminogen, is a clinically meaningful cardiovascular risk marker in women. There is also poor agreement among lipoprotein(a) levels obtained by different assays.

Objective To determine the association of lipoprotein(a) levels, measured with an assay independent of apolipoprotein(a) isoform size, with the incidence of future cardiovascular events.

Design, Setting, and Participants Prospective study of 27 791 initially healthy women in the Women's Health Study, enrolled between November 1992 and July 1995 and followed up for 10 years. Lipoprotein(a) level was measured in blood samples obtained at baseline with an assay independent of apolipoprotein(a) isoform size.

Main Outcome Measure Hazard ratios (HRs) for first-ever major cardiovascular events (nonfatal myocardial infarction, nonfatal cerebrovascular event, coronary revascularization, or cardiovascular deaths).

Results During follow-up, there were 899 incident cardiovascular events. After adjusting for age, smoking, blood pressure, body mass index, total cholesterol, high-density lipoprotein cholesterol, diabetes, hormone use, C-reactive protein, and randomization treatment groups, women in the highest quintile of lipoprotein(a) (≥ 44.0 mg/dL) were 1.47 times more likely (95% CI, 1.21-1.79; *P* for trend $< .001$) to develop cardiovascular events than women in the lowest quintile (≤ 3.4 mg/dL). This association, however, was due almost entirely to a threshold effect among those with the highest lipoprotein(a) levels. After adjusting for all of the variables listed above, the HR associated with lipoprotein(a) levels exceeding the 90th percentile (≥ 65.5 mg/dL) was 1.66 (95% CI, 1.38-1.99); 95th percentile (≥ 83 mg/dL), 1.87 (95% CI, 1.50-2.34); and 99th percentile (≥ 130.7 mg/dL), 1.99 (95% CI, 1.32-3.00), with almost no risk gradient at lower levels. Associations were strongest among women with low-density lipoprotein cholesterol (LDL-C) above the median level. In this subgroup, the adjusted HR associated with lipoprotein(a) levels exceeding the 90th percentile was 1.81 (95% CI, 1.48-2.23); 95th percentile, 1.93 (95% CI, 1.51-2.48); and 99th percentile, 1.93 (95% CI, 1.21-3.05) (*P* value for interaction with LDL-C = .001).

Conclusions In this cohort of initially healthy women, extremely high levels of lipoprotein(a) (≥ 90 th percentile), measured with an assay independent of apolipoprotein(a) isoform size, were associated with increased cardiovascular risk, particularly in women with high levels of LDL-C. However, the threshold and interaction effects observed do not support routine measurement of lipoprotein(a) for cardiovascular stratification in women.

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been due to the poor agreement between lipoprotein(a) levels obtained by different lipoprotein(a) assays in clinical studies. Recently, however, an assay that uses a latex-enhanced immunoturbidimetric method, independently of apolipoprotein(a) isoform size and kringle IV type-2 repeats,^{27,28} has become available.

Further complications regarding interpretation of lipoprotein(a) levels have derived from differences in sex,^{9,29,30} ethnicity,⁹ and differing sensitivities of stored lipoprotein(a) to degradation, often in an apolipoprotein(a) isoform-dependent manner,^{31,32} making direct comparison of lipoprotein(a) studies challenging.^{33,34} Whether relationships of lipoprotein(a) to cardiovascular risk are linear or apply in a threshold manner to those with the highest levels also remains controversial.

To address these issues, we used a state-of-the-art lipoprotein(a) assay to evaluate the role of baseline lipoprotein(a) level among 27 791 initially healthy women who were followed up for 10 years for incident cardiovascular events. We also evaluated, based on prior evidence,^{8,35-39} whether lipoprotein(a) interacts with LDL-C to affect cardiovascular events in women. Finally, because lipoprotein(a) is often measured in patients with premature coronary artery disease, lipoprotein(a) levels in those with and without such family history were compared.

METHODS

Study Design

The study cohort was derived from participants in the Women's Health Study, a randomized, double-blind, placebo-controlled, 2 × 2 factorial design trial of aspirin and vitamin E in the prevention of cardiovascular disease and cancer, conducted among initially healthy women aged 45 years or older.⁴⁰⁻⁴² Participants, enrolled between November 1992 and July 1995, provided baseline information on behavioral, lifestyle, and demographic risk factors. All participants were followed up prospectively for 10 years for the occurrence

of first-ever major cardiovascular events, including nonfatal myocardial infarction (MI), nonfatal stroke, coronary revascularization procedures, and cardiovascular-related death. The methods of the cohort assembly, follow-up, and end-point validation have been described previously.⁴⁰⁻⁴² All participants in the Women's Health Study provided written informed consent and the study protocol was approved by the institutional review board of Brigham and Women's Hospital (Boston, Mass).

Among Women's Health Study participants, 28 345 provided baseline blood samples that were stored in liquid nitrogen (−150°C to −180°C) until the time of analysis. These samples underwent lipoprotein(a) and lipid analysis in a core laboratory certified by the National Heart, Lung, and Blood Institute/Centers for Disease Control and Prevention Lipid Standardization Program. Due to poor agreement between lipoprotein(a) levels obtained by different methods,²⁸ we used the only commercially available assay tested by the National Heart, Lung, and Blood Institute and the International Federation of Clinical Chemistry that is not affected by kringle IV type-2 repeats.²⁸ We determined the concentration of lipoprotein(a) using a turbidimetric assay on the Hitachi 917 analyzer (Roche Diagnostics, Indianapolis, Ind), using reagents and calibrators from Denka Seiken (Tokyo, Japan). The day-to-day variability of lipoprotein(a) concentrations of 17.6 and 58.1 mg/dL were 3.6% and 1.5%, respectively.

High-sensitivity C-reactive protein (CRP) was measured using a validated immunoturbidimetric method (Denka Seiken).⁴³ Total cholesterol was measured enzymatically. High-density lipoprotein cholesterol (HDL-C) (Roche Diagnostics, Basel, Switzerland) and LDL-C (Genzyme, Cambridge, Mass) were measured by a homogeneous direct method. All lipid determinations were performed on the Hitachi 917 autoanalyzer. Ninety-eight percent of the samples received by the core laboratory underwent successful evaluation for each biomarker.

Statistical Analysis

Because the distribution of lipoprotein(a) was right-skewed, median values were computed and ranked tests were used to determine differences according to baseline characteristics (Kruskal-Wallis test for 3 groups and Wilcoxon rank sum test for 2 groups). Spearman correlation coefficients were calculated to discern correlations between lipoprotein(a), other lipid fractions, and high-sensitivity CRP. We divided the population according to quintiles of lipoprotein(a) levels and assessed the hazard ratios (HRs) of future cardiovascular events in Cox proportional hazards models, comparing quintiles 2 through 5 with the lowest (referent) quintile. The HRs were estimated in models adjusting for age only and in models adjusting for age (in years), blood pressure (systolic/diastolic as defined by Framingham risk models: <120/<75 mm Hg; 120-129/75-84 mm Hg; 130-139/85-89 mm Hg; 140-159/90-94 mm Hg; and ≥160/≥95 mm Hg), diabetes, current smoking status, body mass index (as defined by World Health Organization categories: <25, 25-29.9, ≥30), current hormone therapy status (current use vs past or never use), total cholesterol, HDL-C, CRP, and randomization treatment groups. Tests for trends across quintiles of lipoprotein(a) were addressed by entering a single ordinal term for each quintile based on the median value for lipoprotein(a) within each quintile. To evaluate for evidence of threshold effects between increasing levels of lipoprotein(a) and risk of future cardiovascular events, we then used prespecified cutoffs at the 25th, 50th, 75th, 90th, 95th, and 99th percentiles of baseline lipoprotein(a) levels, calculating HRs for individuals with lipoprotein(a) levels exceeding each of these thresholds.

To assess for interaction between lipoprotein(a) and LDL-C, and to assess for joint effects, we calculated the HRs of future cardiovascular events in Cox proportional hazard models after dividing the cohort into 4 groups for lipoprotein(a) levels at, above, or less than the

90th percentile (65.5 mg/dL) and LDL-C levels at, above, or less than the median (121.4 mg/dL). *P* values for interaction were computed. We constructed Kaplan-Meier curves for incident cardiovascular events with lipoprotein(a) levels at, above, or less than the 90th percentile and with or without a family history of MI in a parent before the age of 60 years. Finally, right-censored *c* statistic values⁴⁴ were calculated for models that did and did not include lipoprotein(a). All *P* values are 2-tailed and a value of less than .05 is considered significant. Data analysis was conducted using SAS statistical software version 9.1 (SAS Institute Inc, Cary, NC) and S-PLUS version 6.0 (Insightful Corp, Seattle, Wash).

RESULTS

At study entry, the mean (SD) age of the 27 791 women was 54.2 (7.1) years. They had a mean (SD) body mass index (calculated as weight in kilograms divided by height in meters squared) of 25.9 (5). A total of 3218 smoked currently, 782 had diabetes, 6975 had hypertension, and 3210 had a family history of MI in a parent before the age of 60 years. A total of 899 women developed first-ever cardiovascular events. There were 232 nonfatal MIs, 244 nonfatal ischemic cerebrovascular events, 560 coronary revascularizations (percutaneous angioplasty or coronary artery bypass grafting), and 142 cardiovascular deaths; for women

with multiple events, only the first was considered for this analysis.

The distribution of lipoprotein(a) levels at baseline for the complete study population and according to other cardiovascular risk factors is presented in TABLE 1. A total of 7345 (26.4%) women had lipoprotein(a) levels of 30 mg/dL or higher—a level often used for conveying increased risk.^{16,45,46} Women who had diabetes or were taking hormone therapy had lower lipoprotein(a) levels (*P*<.001), whereas higher lipoprotein(a) levels were found among women who were older (*P*<.001), black (*P*<.001), or reported a family history of myocardial disease before the age of 60 years

Table 1. Distribution of Lipoprotein(a) Levels at Study Entry Among Apparently Healthy Women and Within Indicated Subgroups

	No. of Women	Lipoprotein(a) Levels, mg/dL, at Each Distribution Percentile						
		5th	10th	25th	50th	75th	90th	95th
Lipoprotein(a) level, median, mg/dL	27 791	1.30	1.90	4.40	10.60	32.80	65.50	83.00
Age, in decades, y								
38-49	8875	1.30	1.90	4.40	10.20	30.40	61.80	79.50
50-59	12 817	1.30	1.80	4.30	10.50	33.00	66.50	83.80
60-69	5165	1.30	2.00	4.70	11.50	35.80	68.10	85.00
70-89	934	1.50	2.10	5.20	12.35	35.00	71.00	88.60
Body mass index*								
<25	14 087	1.30	1.90	4.40	10.30	31.50	64.80	82.10
25-29.9	8355	1.30	1.90	4.50	11.00	34.00	66.90	85.00
≥30	4810	1.20	1.80	4.30	10.90	33.80	65.30	82.00
Framingham systolic/diastolic blood pressure categories, mm Hg								
<120/<75	9235	1.30	1.90	4.60	10.40	31.70	63.40	80.60
120/75 to 129/84	8863	1.30	1.90	4.40	10.60	31.80	65.50	84.30
130/85 to 139/89	5176	1.30	1.90	4.50	11.10	35.05	67.30	82.30
140/90 to 159/94	3599	1.20	1.80	4.20	11.00	32.90	67.60	85.00
≥160/≥95	599	1.10	1.70	4.10	10.10	35.40	67.40	84.20
Smoking history								
Current	3218	1.30	1.80	4.30	10.50	32.40	66.60	84.70
Past or never	24 549	1.30	1.90	4.40	10.60	32.90	65.40	82.70
Diabetes history								
Yes	782	1.00	1.50	3.30	9.10	29.90	68.30	91.80
No	26 996	1.30	1.90	4.50	10.70	32.90	65.40	82.60
Hormone therapy								
Current	12 075	1.20	1.70	3.90	9.40	30.40	64.40	81.70
Past or never	15 661	1.40	2.10	4.90	11.60	34.30	66.30	83.90
Race/ethnicity								
White	26 261	1.30	1.90	4.30	10.30	31.80	65.20	82.40
Black	513	4.70	7.60	17.60	34.90	63.00	96.80	117.30
Other	781	1.40	2.10	4.80	10.60	25.80	52.00	66.20
Family history of myocardial infarction								
Yes	3210	1.20	1.90	4.60	11.30	37.50	71.00	88.20
No	21 798	1.30	1.90	4.30	10.40	31.30	64.30	81.70

*The World Health Organization categories were used. Body mass index is calculated as weight in kilograms divided by height in meters squared.

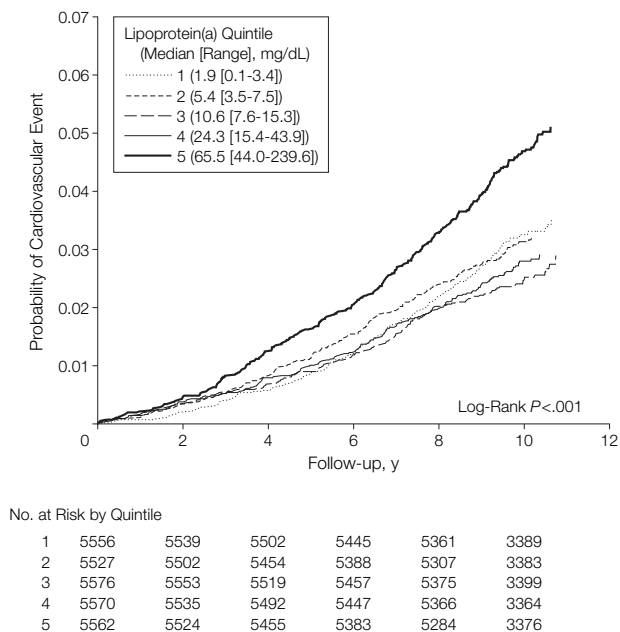
Table 2. Future Cardiovascular Events Among Initially Healthy Women According to Lipoprotein(a) Quintiles at Study Entry

	Lipoprotein(a) Quintiles at Study Entry					P Value for Trend
	1	2	3	4	5	
Lipoprotein(a) level, median (range), mg/dL	1.90 (0.10-3.40)	5.40 (3.50-7.50)	10.60 (7.60-15.30)	24.30 (15.40-43.90)	65.50 (44.00-239.60)	
Cardiovascular events, No. (%)	178 (3.2)	169 (3.1)	140 (2.5)	152 (2.7)	260 (4.7)	
Person-years of follow-up	55 062	54 612	55 228	55 045	54 626	
HR (95% CI)						
Age-adjusted	1.00	0.98 (0.79-1.21)	0.77 (0.62-0.96)	0.81 (0.66-1.01)	1.41 (1.17-1.71)	<.001
Framingham covariate-adjusted*	1.00	1.00 (0.81-1.24)	0.76 (0.61-0.95)	0.77 (0.62-0.96)	1.35 (1.12-1.64)	<.001
Fully adjusted†	1.00	1.07 (0.86-1.32)	0.83 (0.66-1.04)	0.86 (0.69-1.08)	1.47 (1.21-1.79)	<.001

Abbreviations: CI, confidence interval; HR, hazard ratio.

*Adjusted for age, blood pressure categories, current smoking status, total cholesterol, and high-density lipoprotein cholesterol.

†Adjusted for age, blood pressure categories, current smoking status, total cholesterol, high-density lipoprotein cholesterol, body mass index, diabetes, current hormone therapy use, C-reactive protein, and randomization treatment group.

Figure 1. Probability of Cardiovascular Events According to Increasing Quintiles of Lipoprotein(a) Levels

($P < .001$). No significant relationships were discerned between lipoprotein(a) level and body mass index, blood pressure, or smoking status.

The Spearman correlation coefficient between lipoprotein(a) and apolipoprotein A-1 was -0.02 ($P < .001$); apolipoprotein B, 0.14 ($P < .001$); total cholesterol, 0.14 ($P < .001$); LDL-C, 0.17 ($P < .001$); HDL-C, 0.003 ($P = .61$); and non-HDL-C (total cholesterol minus HDL-C), 0.13 ($P < .001$); and high-sensitivity CRP, -0.007 ($P = .22$).

Association of Lipoprotein(a) With Cardiovascular Events

The age-adjusted and fully adjusted HRs for future cardiovascular events according to quintiles of lipoprotein(a) are presented in TABLE 2. In analyses controlling for age, smoking, blood pressure, body mass index, total cholesterol, HDL-C, diabetes, hormone use, CRP, and randomization treatment groups, women in the highest quintile of lipoprotein(a) (≥ 44.0 mg/dL) were 1.47 times more likely (95% confi-

dence interval [CI], 1.21-1.79) to develop cardiovascular events than women in the lowest quintile (≤ 3.4 mg/dL; P for trend $< .001$). However, as shown in FIGURE 1, this association was almost entirely seen in the top quintile suggesting a threshold effect (log-rank $P < .001$). Similar associations were seen for coronary heart disease (MI, death due to cardiovascular causes, coronary revascularization) and ischemic stroke. In the fully adjusted models, women in the top quintile of lipoprotein(a) had a 1.35 times higher HR (95% CI, 1.07-1.71; $P < .001$ for trend across quintiles) for coronary heart events compared with the lowest quintile and a 1.87 times higher HR (95% CI, 1.29-2.71; $P = .003$ for trend across all quintiles) for ischemic stroke compared with the lowest quintile.

The HRs for prespecified thresholds of lipoprotein(a) were calculated and are shown in TABLE 3. The multivariate-adjusted HR in women with lipoprotein(a) levels higher than the 90th percentile was 1.66 ($P < .001$); 95th percentile, 1.87 ($P < .001$); and 99th percentile, 1.99 ($P = .001$). After additional adjustment for race/ethnicity (white, black, other), similar trends were seen.

Interaction Between Elevated Lipoprotein(a) and Elevated LDL-C on Cardiovascular Events

The rates of incident cardiovascular disease according to lipoprotein(a) levels at, above, or less than the 90th percentile and LDL-C levels at, above, or less than the study median value of 121.4

Table 3. Future Cardiovascular Events Among Initially Healthy Women According to Prespecified Thresholds of Lipoprotein(a)

Cutoff Percentile	Lipoprotein(a) Level, mg/dL	No. of Women	Cardiovascular Events, No. (%)	Age-Adjusted HR (95% CI)	P Value	Fully Adjusted HR (95% CI)*	P Value
25th	≥4.4	20957	682 (3.3)	1.00 (0.86-1.16)	.97	1.05 (0.90-1.23)	.56
50th	≥10.6	13955	488 (3.5)	1.12 (0.98-1.28)	.09	1.10 (0.96-1.27)	.15
75th	≥32.8	6953	302 (4.3)	1.48 (1.29-1.70)	<.001	1.48 (1.29-1.71)	<.001
90th	≥65.5	2783	154 (5.5)	1.76 (1.48-2.09)	<.001	1.66 (1.38-1.99)	<.001
95th	≥83	1390	92 (6.6)	2.12 (1.71-2.63)	<.001	1.87 (1.50-2.34)	<.001
99th	≥130.7	279	24 (8.6)	2.58 (1.72-3.87)	<.001	1.99 (1.32-3.00)	.001

Abbreviations: CI, confidence interval; HR, hazard ratio.

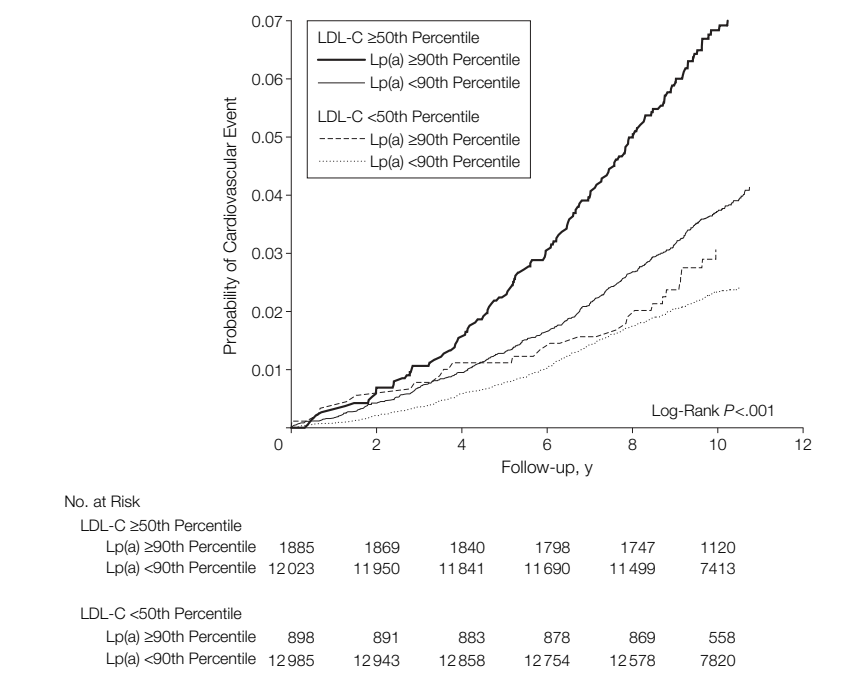
*Adjusted for age, blood pressure categories, current smoking status, total cholesterol, high-density lipoprotein cholesterol, body mass index, diabetes, current hormone use, C-reactive protein, and randomization treatment group.

mg/dL are presented in FIGURE 2. The highest rates of cardiovascular disease are seen in women with both lipoprotein(a) levels at or above the 90th percentile and LDL-C levels at or above the median. The cohort was further stratified by median LDL-C levels (TABLE 4). A 1.64-times higher fully adjusted HR for cardiovascular events was seen in the top lipoprotein(a) quintile compared with the bottom quintile with LDL-C levels at or above the median ($P<.001$ for trend across all quintiles). In contrast, these associations were not seen in the women with LDL-C levels below the median.

The threshold analysis in the subset of women with LDL-C levels at or above the median showed a fully adjusted HR of 1.81 (95% CI, 1.48-2.23) for lipoprotein(a) levels above the 90th percentile ($P<.001$); 1.93 (95% CI, 1.51-2.48) for levels above the 95th percentile ($P<.001$); and 1.93 (95% CI, 1.21-3.05) for levels above the 99th percentile ($P=.005$). A P value of .001 was observed in a formal test for interaction, cutting the lipoprotein(a) and LDL-C categories by their median values to increase statistical power.

Family History of Premature MI and Lipoprotein(a)

To evaluate whether family history affects the association of lipoprotein(a) with cardiovascular disease in these data, we stratified our analyses by family status. Lipoprotein(a) levels were in general higher in women with a family history of premature MI than in those without such a history (median lipoprotein(a) levels, 11.30 vs 10.40 mg/dL, respectively, $P<.001$; Table 1). How-

Figure 2. Lipoprotein(a) and Low-Density Lipoprotein Cholesterol Levels and Cardiovascular Disease

LDL-C indicates low-density lipoprotein cholesterol; Lp(a), lipoprotein(a).

ever, when comparing the highest lipoprotein(a) quintile with the lowest quintile, the adjusted HRs were similar among women with a family history of premature MI (1.51; 95% CI, 0.87-2.63) and without such a history (1.47; 95% CI, 1.17-1.85). Women with high lipoprotein(a) levels had a higher risk of cardiovascular disease, regardless of family history.

Analysis With C Statistic

The right-censored concordance index (c statistic) for the fully adjusted model that included lipoprotein(a) level was 0.80. When lipoprotein(a) level was

removed from this model, the c statistic was 0.79. This effect, while small, was similar in magnitude to parallel models that excluded total cholesterol (0.79), HDL-C (0.79), smoking status (0.78), or blood pressure (0.79).

COMMENT

In this large prospective cohort study of initially healthy women, extremely high levels of lipoprotein(a), measured with an assay independent of apolipoprotein(a) isoform size, were associated with increased cardiovascular disease risk, particularly in women with high LDL-C levels. This relationship ex-

isted independently of traditional risk markers, and CRP. However, these results were driven almost exclusively by extremely elevated lipoprotein(a) levels among those with above median LDL-C levels, with almost no risk gradient in individuals with lower lipoprotein(a) levels, which constituted the majority of individuals screened. The interaction seen between lipoprotein(a) and LDL-C levels in our study is in concordance with recent biological data that point to the modification of the atherogenicity of lipoprotein(a) by interaction with oxidized LDL-C⁶ and with clinical data from a number of prior case-control and cohort studies.^{8,35-39}

The current data may help to address some of the controversy that has stemmed from some prior studies of lipoprotein(a). As we did not see a linear effect in this data, it is possible that prior studies that did not evaluate for thresholds^{29,47} may have missed modest but significant lipoprotein(a) effects on cardiovascular risk. Second, in contrast to several prior studies,^{22,25,29} we also assessed for the interaction of lipoprotein(a) with LDL-C and found the risk

to be largest among those with concomitant increases in LDL-C levels. Third, we used a newly available lipoprotein(a) assay, that unlike other assays, has been validated by a program for the standardization of lipoprotein(a) measurements supported by the National Heart, Lung, and Blood Institute and the International Federation of Clinical Chemistry.²⁸ Fourth, our data raise the possibility that traditional clinical thresholds for lipoprotein(a) are too low. Risk increased when levels exceeded 65.5 mg/dL, which is a level much higher than the previously suggested cut point of 30 mg/dL.⁴⁸

While of pathophysiological interest, we do not believe our data support generalized screening of lipoprotein(a) in the population as a whole because only extremely high levels were associated with cardiovascular risk. Clinically, lipoprotein(a) level is not lowered by most lipid-correcting therapies with the exception of high doses of nicotinic acid (3-4 g/d), a dose that requires close monitoring and is poorly tolerated. Furthermore, there is no clinical evidence that lowering lipoprotein(a) levels lowers cardiovas-

cular risk. However, aggressive lowering of LDL-C levels has been shown to be important in modifying the excess cardiovascular risk associated with elevated lipoprotein(a) levels,⁴⁹ suggesting that when lipoprotein(a) levels are elevated, the primary objective should be to treat elevated LDL-C aggressively either with a statin or with niacin. Determination of lipoprotein(a) levels should thus be reserved for high-risk subsets of the population such as individuals with premature MI who have otherwise normal risk profiles or are at particularly high risk because of circumstances such as familial hypercholesterolemia.⁵⁰

Strengths of our prospective cohort study include its size, the storage conditions of the samples, and the assay used. In this regard, our cohort study helps to resolve mixed results based on sparse data in women³⁰ and from studies that may have been inconclusive due to small sample size.⁵¹⁻⁵³ Second, our samples were stored in liquid nitrogen until the time of this study, without multiple freeze-thaw cycles that can potentially alter lipoprotein(a) levels.³² Third, the assay used was inde-

Table 4. Cardiovascular Events by Lipoprotein(a) Quintiles, Stratified by Low-Density Lipoprotein Cholesterol Levels

	Lipoprotein(a) Quintile Median (Range), mg/dL*					P Value for Trend
	1 1.90 (0.10-3.40)	2 5.40 (3.50-7.50)	3 10.60 (7.60-15.30)	4 24.30 (15.40-43.90)	5 65.50 (44.00-239.60)	
LDL Cholesterol \geq50th Percentile (\geq121 mg/dL) (n = 13908)						
Cardiovascular events, No. (%)	97 (4.1)	85 (3.4)	88 (3.3)	102 (3.4)	205 (6.1)	
Person-years of follow-up	23 175	24 441	26 678	29 753	33 065	
HR (95% CI)						
Age-adjusted	1.00	0.85 (0.63-1.13)	0.78 (0.58-1.04)	0.78 (0.59-1.03)	1.46 (1.15-1.86)	<.001
Framingham covariate-adjusted†	1.00	0.86 (0.64-1.16)	0.76 (0.57-1.02)	0.75 (0.57-1.00)	1.49 (1.17-1.90)	<.001
Fully adjusted‡	1.00	0.93 (0.69-1.26)	0.87 (0.65-1.17)	0.87 (0.65-1.16)	1.64 (1.28-2.11)	<.001
LDL Cholesterol <50th Percentile (<121 mg/dL) (n = 13883)						
Cardiovascular events, No. (%)	81 (2.5)	84 (2.8)	52 (1.8)	50 (2.0)	55 (2.5)	
Person-years of follow-up	31 887	30 170	28 550	25 292	21 561	
HR (95% CI)						
Age-adjusted	1.00	1.14 (0.84-1.55)	0.71 (0.50-1.00)	0.80 (0.56-1.13)	1.01 (0.72-1.42)	.96
Framingham covariate-adjusted†	1.00	1.20 (0.88-1.63)	0.76 (0.54-1.08)	0.85 (0.59-1.21)	1.05 (0.74-1.49)	.95
Fully adjusted‡	1.00	1.26 (0.92-1.72)	0.77 (0.54-1.11)	0.88 (0.61-1.26)	1.11 (0.78-1.58)	.77

Abbreviations: CI, confidence interval; HR, hazard ratio; LDL, low-density lipoprotein.

*Quintile values were derived from the entire cohort.

†Adjusted for age, blood pressure categories, current smoking status, total cholesterol, and high-density lipoprotein cholesterol.

‡Adjusted for age, blood pressure categories, current smoking status, total cholesterol, high-density lipoprotein cholesterol, body mass index, diabetes, current hormone use, C-reactive protein, and randomization treatment group.

pendent of both kringle IV type-2 repeats and apolipoprotein(a) isoform size.

Limitations of our data include the predominant white ethnicity of our cohort. There may be important racial and ethnic differences in lipoprotein(a) levels and effects on cardiovascular disease that we were not able to assess in our study. Additionally, lipoprotein(a) may be associated with premature atherosclerosis, an issue we cannot fully address as the average age of our cohort at inception was 54.2 years.

In summary, in this prospective cohort of 27 791 initially healthy women, we found that very high levels of lipoprotein(a) measured with an assay independent of apolipoprotein(a) isoform size were predictive of future cardiovascular events, particularly when LDL-C level was also high. While the threshold effects seen do not support generalized screening, our data do indicate that lipoprotein(a) may have clinical importance for selected high-risk women.

Author Contributions: Dr Suk Danik had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Suk Danik, Ridker.

Acquisition of data: Buring, Ridker.

Analysis and interpretation of data: Suk Danik, Rifai, Buring, Ridker.

Drafting of the manuscript: Suk Danik, Ridker.

Critical revision of the manuscript for important intellectual content: Suk Danik, Rifai, Buring, Ridker.

Statistical analysis: Suk Danik.

Obtained funding: Suk Danik, Buring, Ridker.

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Study supervision: Ridker.

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The final purpose of art is to intensify, even, if necessary, to exacerbate, the moral consciousness of people.

—Norman Mailer (1923-)