Race Is a Key Variable in Assigning Lipoprotein(a) Cutoff Values for Coronary Heart Disease Risk Assessment
The Multi-Ethnic Study of Atherosclerosis

Weihua Guan, Jing Cao, Brian T. Steffen, Wendy S. Post, James H. Stein, Mathew C. Tattersall, Joel D. Kaufman, Joseph P. McConnell, Daniel M. Hoefner, Russell Warnick, Michael Y. Tsai

Objective—We aimed to examine associations of lipoprotein(a) (Lp(a)) concentrations with coronary heart disease (CHD) and determine whether current Lp(a) clinical laboratory cut points identify risk of disease incidence in 4 races/ethnicities of the Multi-Ethnic Study of Atherosclerosis (MESA).

Approach and Results—A subcohort of 1323 black, 1677 white, 548 Chinese American, and 1044 Hispanic MESA participants were followed up during a mean 8.5-year period in which 235 incident CHD events were recorded. Lp(a) mass concentrations were measured using a turbidimetric immunoassay. Cox regression analysis determined associations of Lp(a) with CHD risk with adjustments for lipid and nonlipid variables. Lp(a) concentrations were continuously associated with risk of CHD incidence in black (hazard ratio [HR], 1.49; 95% confidence interval [CI], 1.09–2.04) and white participants (HR, 1.22; 95% CI, 1.02–1.45). Examining Lp(a) risk by the 50 mg/dL cut point revealed higher risks of incident CHD in all races except Chinese Americans: blacks (HR, 1.69; 95% CI, 1.03–2.76), whites (HR, 1.82; 95% CI, 1.15–2.88); Hispanics (HR, 2.37; 95% CI, 1.17–4.78). The lower Lp(a) cut point of 30 mg/dL identified higher risk of CHD in black participants alone (HR, 1.87; 95% CI, 1.08–3.21).

Conclusions—Our findings suggest that the 30 mg/dL cutoff for Lp(a) is not appropriate in white and Hispanic individuals, and the higher 50 mg/dL cutoff should be considered. In contrast, the 30 mg/dL cutoff remains suitable in black individuals. Further research is necessary to develop the most clinically useful Lp(a) cutoff values in individual races/ethnicities. (Arterioscler Thromb Vasc Biol. 2015;35:00-00. DOI: 10.1161/ATVBAHA.114.304785.)

Key Words: continental population groups ■ coronary disease ■ lipoprotein(a) ■ risk factor

The American Heart Association/American College of Cardiology task force has recently issued guidelines for assessing 10-year atherosclerotic cardiovascular disease risk.1 Within these guidelines, it is acknowledged that the risk algorithm for predicting disease remains imperfect, and further research is needed to improve risk evaluation—particularly in areas relating to genetic hyperlipidemias in Hispanic and Asian populations. To address this shortfall, the present study examines whether the lipid carrying particle, lipoprotein(a) (Lp(a)), imposes risk of incident coronary heart disease (CHD) across 4 race/ethnic groups in the Multi-Ethnic Study of Atherosclerosis (MESA).

Lp(a) is a well-studied subspecies of low-density lipoprotein that is recognized as a significant risk factor for CHD;2–9 and findings from a Mendelian randomization study suggest that elevated Lp(a) may directly contribute to CHD development.10 Distinguishing it from other apolipoprotein B–containing lipoproteins, Lp(a) blood concentrations are primarily determined by the apo(a) gene, LPA,11,12 and are negligibly affected by lifestyle modifications, such as diet and exercise.9 As a consequence of this strong genetic influence, race-based disparities in Lp(a) concentrations have been documented. Studies have consistently shown that black individuals have 2- to 3-fold higher Lp(a) levels than whites in numerous case–control and prospective studies.2,4,5,13–14 Although fewer studies have been conducted in Chinese and Hispanic populations, it has been shown that Chinese have lower Lp(a) levels than whites,15 whereas inconsistent results have been reported in Hispanics.5,16,17

In addition to the race-based differences in Lp(a), it remains unclear whether elevated Lp(a) levels impose a significant risk of CHD across different races/ethnicities. Indeed, it has been observed that black individuals have a substantially higher median level of Lp(a), but a correspondingly higher incidence of CHD is not observed,18 which suggests that Lp(a) does not impose the degree of CHD risk in blacks as it does in whites.
This disparity between blacks and whites may necessitate race-specific Lp(a) cut points and re-evaluation of the existing 30 mg/dL cut point used by practitioners and clinical laboratories across the US. Supporting the latter, a recommendation by the 2010 European Atherosclerosis Society Consensus Panel advocates a higher cut point of 50 mg/dL.

Given the discrepancies in the literature and the limited research conducted in Hispanic and Chinese populations, we aimed to examine racial/ethnic differences in (1) Lp(a) mass levels and distribution patterns; (2) associations of Lp(a) with incident CHD; (3) the use of existing 30 or 50 mg/dL cut points in identifying CHD risk in a prospective study of Hispanic MESA participants during a median 8.5-year follow-up period.

## Materials and Methods

Materials and Methods are available in the online-only Data Supplement.

## Results

Characteristics of MESA participants across the 4 races/ethnic groups at baseline are shown in Table 1. The age and sex distributions at baseline are comparable. Blacks had the highest median level of Lp(a) compared with Hispanics, Chinese Americans, or whites. Distributions of Lp(a) in blacks, whites, Chinese Americans, and Hispanics are shown in the Figure. Lp(a) levels in all ethnic groups were right-skewed although the black population showed less skewness. The median levels of Lp(a) for the 4 groups were blacks, 35.1 mg/dL; whites, 13.0 mg/dL; Chinese, 12.9 mg/dL; and Hispanics, 13.1 mg/dL.

Associations between baseline Lp(a) levels and CHD incidence >8.5 years of follow-up are shown in Table 2. Lp(a) was log-transformed to account for non-normal distributions. For all 4593 participants, 1 U increase in log-Lp(a) led to a significantly higher risk of developing CHD (hazard ratio [HR], 1.26; 95% confidence interval [CI], 1.11–2.03) after adjusting for race/ethnicity and other CHD risk factors, including age, sex, education, smoking, hypertension medication, systolic blood pressure, diabetes mellitus, race, high-density lipoprotein-cholesterol, non-Lp(a) low-density lipoprotein-cholesterol, and log-triglycerides. After stratifying the subcohort by race/ethnicity, black individuals showed an association between Lp(a) and CHD incidence (HR, 1.49; 95% CI, 1.09–2.04), as well as whites (HR, 1.22; 95% CI, 1.02–1.45). No significant associations were found in Chinese Americans (HR, 1.08; 95% CI, 0.65–1.80) or Hispanics (1.14; 95% CI, 0.86–1.50).

Further analyses were performed using 2 cut points for Lp(a) (Table 3). Lp(a) levels ≥30 mg/dL revealed higher CHD risk in all races except Chinese Americans: Hispanics (HR, 2.37; 95% CI, 1.17–4.78); blacks (HR, 1.69; 95% CI, 1.03–2.76), whites (HR, 1.82; 95% CI, 1.15–2.88). In contrast, only black participants showed significant risk of CHD in those with Lp(a) levels ≥50 mg/dL (HR, 1.87; 95% CI, 1.08–3.21).

Net reclassification index (NRI) scores and c-statistics were assessed to determine whether adding Lp(a) to a baseline risk model would more accurately predict CHD cases and non-cases in black, white, Chinese, and Hispanic participants, as well as in the population as a whole. Models treating Lp(a) as a continuous (per 1 log unit increase) or categorical variable (>30 or >50 mg/dL) are presented in Table 1 in the online-only Data Supplement. Significant NRI results were observed where Lp(a) >30 mg/dL in black individuals and the entire subcohort. The significant improvement in reclassification was driven largely by correctly predicting a higher risk in those who had events: 73% or 48 cases in black participants.

## Table 1. Characteristics of Multi-Ethnic Study of Atherosclerosis (MESA) Participants in 4 Ethnic Groups at Visit 1

<table>
<thead>
<tr>
<th></th>
<th>Blacks (n=1323)</th>
<th>Whites (n=1677)</th>
<th>Chinese Americans (n=548)</th>
<th>Hispanics (n=1044)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>61 (52–70)</td>
<td>62 (54–71)</td>
<td>62 (53–71)</td>
<td>61 (52–69)</td>
</tr>
<tr>
<td>Sex (men)</td>
<td>621 (46.1%)</td>
<td>813 (47.6%)</td>
<td>217 (38.8%)</td>
<td>517 (48.6%)</td>
</tr>
<tr>
<td>Smoker</td>
<td>726 (53.9%)</td>
<td>929 (54.4%)</td>
<td>137 (24.5%)</td>
<td>504 (47.4%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>196 (14.6%)</td>
<td>86 (5.0%)</td>
<td>55 (9.8%)</td>
<td>171 (16.1%)</td>
</tr>
<tr>
<td>Hypertensive</td>
<td>428 (31.8%)</td>
<td>325 (19.0%)</td>
<td>126 (22.5%)</td>
<td>257 (24.2%)</td>
</tr>
<tr>
<td>On hypertension medicine</td>
<td>613 (45.5%)</td>
<td>493 (28.8%)</td>
<td>138 (24.7%)</td>
<td>305 (28.7%)</td>
</tr>
<tr>
<td>Non-Lp(a) LDL-C, mg/dL</td>
<td>113 (92–133)</td>
<td>115 (97–136)</td>
<td>114 (96–132)</td>
<td>116 (97–137)</td>
</tr>
<tr>
<td>HDL-C, mg/dL</td>
<td>50 (41–61)</td>
<td>50 (41–62)</td>
<td>48 (40–58)*</td>
<td>45 (38–54)*</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>89 (66–122)*</td>
<td>110 (75–160)*</td>
<td>121 (85–169)*</td>
<td>133 (84–189)*</td>
</tr>
<tr>
<td>Lp(a), mg/dL</td>
<td>35.1 (20.4–61.6)*</td>
<td>12.9 (5.8–29.6)</td>
<td>12.9 (7.7–23.4)</td>
<td>13.1 (6.3–28.8)*</td>
</tr>
</tbody>
</table>

Median values (interquartile range) are specified for continuous variables and (%) for categorical variables. Median values are shown for triglycerides and Lp(a). smoker is former or current; diabetic is treated or untreated; hypertensive is systolic blood pressure ≥140 mm Hg. HDL-C indicates high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; and Lp(a), lipoprotein(a).

*Significantly different (P<0.05) from all 3 other ethnic groups.
using this cutoff also incorrectly predicted a lower risk in those who did not have events: 55% or 692 noncases in black individuals and 32% or 1394 noncases for the subcohort.

In contrast, improvements in \(c\)-statistics were observed across all models for the vast majority of races/ethnicities (Table I in the online-only Data Supplement). The largest \(c\)-statistic improvement was observed in whites, where \(Lp(a) > 50 \text{ mg/dL} \) (0.011). The lowest \(c\)-statistic improvements were observed in Chinese participants using either cutoff value or \(Lp(a) \) (0.001 for 50 mg/dL; 0.002 for 30 mg/dL) and in Hispanic individuals where \(Lp(a) > 30 \text{ mg/dL} \) cutoff (0.001).

To further test which cutoff value more accurately reflects the relationship between \(Lp(a)\) and CHD events within each race, log-likelihoods of both Cox regression models were compared. In the entire population (n=4593), increasing the \(Lp(a)\) cutoff from 30 to 50 mg/dL resulted in a 2 U increase in log-likelihood. Similarly, changing the cutoff from 30 to 50 mg/dL in whites and Hispanics resulted in an increase of 1.6 and 1.9, respectively. In black participants, the higher 50 mg/dL cutoff resulted in a decrease of 0.6 compared with the 30 mg/dL cutoff although the difference may not be significant.

**Discussion**

In this prospective study of 4593 MESA participants, we aimed to determine whether \(Lp(a)\) levels associate with CHD incidence in Hispanic, black, white, and Chinese participants during a median study follow-up period of 8.5 years. We found that \(Lp(a)\) was associated with higher risk of CHD in all participants; however, after stratifying the population by race/ethnicity, significant association only remained in black and white subgroups. Further analyses using \(Lp(a)\) cut points revealed that 50 mg/dL identified higher CHD risk in all races except Chinese Americans, whereas the 30 mg/dL cut point detected a significant risk of CHD in black study participants alone.

**Lp(a) Levels Across Race/Ethnicity**

It is well-documented that \(Lp(a)\) levels are strongly influenced by race/ethnicity. Black individuals have been shown to have 2- to 3-fold higher median \(Lp(a)\) levels relative to whites in prospective studies and clinical trials—a finding confirmed in this MESA subcohort (median of 35.1 mg/dL in blacks versus 13.0 mg/dL in whites; Table 1). By comparison,
Despite such evidence, guidelines that define normal and elevated at risk levels have yet to be established. Clinical laboratories in the United States generally designate elevated levels at \( \geq 30 \text{ mg/dL} \); however, several investigators and the 2010 European Atherosclerosis Society Consensus Panel recommend that \( 50 \text{ mg/dL} \) serve as the clinical Lp(a) cutoff to signify higher risk of disease. Given this controversy, we tested these early studies of whites,19,20 yet no corresponding research has been conducted in other races. NRI scores are presented for the entire population and only a few studies have been conducted in Hispanic and Asian populations. Haffner et al17 reported significantly lower levels of Lp(a) in 316 Mexican Americans than in 242 whites. In contrast, Kamboh et al16 observed significantly higher Lp(a) levels in 215 Hispanics than in 309 whites. Similar to the MESA population, the Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) trial was composed of 4 races and reported that Lp(a) levels were highest in blacks (n=853; median, 60 \( \text{mg/dL} \)) followed by Asians (n=138; median, 38 \( \text{mg/dL} \)), then Hispanics (n=784; median, 24 \( \text{mg/dL} \)) and finally whites (n=774; median, 23 \( \text{mg/dL} \)). The present analysis supports the JUPITER finding that there are no significant differences in Lp(a) levels between whites and Hispanics. In contrast to JUPITER, we showed no significant differences in Lp(a) levels in Chinese Americans than in white participants; however, it should be recognized that the Asian population in JUPITER was smaller (n=138) than the Chinese American population in this MESA subcohort (n=548), and confirmation is therefore warranted.

Apart from differences in median Lp(a) concentrations, Lp(a) distribution patterns also varied by race (Figure). Whites, Hispanics, and Chinese populations showed right-skewed distribution patterns, whereas the black population showed a relatively more symmetrical distribution pattern with a right-handed tail. These race-based differences in median Lp(a) concentrations and distribution patterns likely have implications for clinical reference ranges and are discussed further below.

### Lp(a) Cutoffs and CHD Risk

Lp(a) has largely been found to be a modest, independent risk factor for CHD and atherothrombotic forms of stroke.5–10 Despite such evidence, guidelines that define normal and elevated risk factors for CHD have implications for clinical reference ranges and are discussed further below.

### Lp(a) in Risk Reclassification

The addition of Lp(a) to CHD risk models has been shown to improve NRI and c-statistics (ie, area under the curve) in previous studies of whites,19,20 yet no corresponding research has been conducted in other races. NRI scores are presented for all 4 race groups across all models (Table I in the online-only Data Supplement), but results are most relevant where HRs of Lp(a) and CHD were found to be significant. Significant NRI scores were only observed in black individuals (P=0.05) and for the entire population (P=0.04), where Lp(a) >30 mg/dL. In contrast, modest increases in c-statistics were observed across all races and models except in Hispanic and Chinese participants, where Lp(a) was treated as a continuous variable. These contrasting NRI and c-statistic results, as well as the inability to replicate previous findings in whites,19,20 are likely because...
of limited statistical power after race-stratification coupled with the modest to moderate influence of Lp(a) on CHD risk. Further investigation is needed in larger, racially diverse populations to determine which cutoff optimally improves risk classification within each race.

**Comparing Lp(a) Cutoff Values Using Log-Likelihood**

Log-likelihood functions have previously been used to determine optimal cutoff values\(^2\) and to compare model fit among data sets. Although P values cannot be directly computed in this type of comparison, a 1 U increase in log-likelihood was used as an a priori threshold that is suggestive of the superior cutoff value. Selecting the higher 50 mg/dL in whites and Hispanics resulted in an increase of 1.6 and 1.9 in log-likelihoods, respectively, signifying that the 50 mg/dL cutoff is a better fit than the 30 mg/dL. In Black participants, however, the higher cutoff of 50 mg/dL resulted in a decrease of 0.6 compared with the 30 mg/dL cutoff, suggesting that 30 mg/dL may serve as the superior cutoff in black individuals although the difference may not be significant because it did not breach the 1 U threshold.

**Lp(a) in Chinese Americans**

Unlike findings in other racial/ethnic groups, no relationship between Lp(a) and CHD was observed in Chinese Americans—in contrast to results from previous studies, albeit in native East Asian populations.\(^22\)-\(^24\) Our null results are likely because of multiple factors, but the relatively fewer number of Chinese participants (n=545) and lower incidence of CHD events (n=18; 3.28%) limited our statistical power for this subgroup. The possibility that a higher Lp(a) cut point would identify CHD risk in Chinese individuals should not be discounted, and follow-up studies in larger Chinese American populations are warranted.

**Strengths and Limitations**

This study provided the first large-scale prospective evaluation of Lp(a) and risk of CHD incidence across 4 major race/ethnic groups in the United States. Despite the limited number of CHD events in this MESA subcohort, particularly after race-stratification, significant relationships between Lp(a) and CHD risk were observed nonetheless. With respect to Lp(a), its immunochemical measurement has historically been challenging because of the variable size of its apo(a) component—a product of the heterogeneity of kringle IV type 2 repeats within apo(a) among individuals. The current study used an Lp(a) assay with antibodies targeted to the uniform region of apo(a) and included 5 apo(a) calibrators with mixed molecular weights to minimize apo(a) size-dependent biases associated with Lp(a) measurement.\(^25\)

In terms of limitations, it should be acknowledged that analyses that included the entire subcohort may have led to an imprecise estimate of the Lp(a)-associated risk of CHD because of racial disparities in triglycerides and blood pressure that may not have been overcome with statistical adjustments. In addition, conflicting results for risk reclassification analyses suggest that further investigation is needed in larger populations to determine which Lp(a) value optimally improves event prediction in individual races. Finally, adjustments were made for multiple confounding variables, but the presence of residual confounders remains possible.

**Conclusions**

The current study provides evidence that race is an important factor when considering the Lp(a) level that imposes a significant risk of CHD development. Our findings suggest that the 30 mg/dL cutoff for Lp(a) is not appropriate in white and Hispanic individuals, and the higher 50 mg/dL cutoff should be considered. In contrast, the 30 mg/dL cutoff remains suitable in black individuals. Further research is necessary to develop the most clinically useful Lp(a) cutoff values in individual races/ethnicities.

**Acknowledgments**

We thank the other investigators, staff, and participants of the Multi-Ethnic Study of Atherosclerosis (MESA) study for their contributions. A full list of participating MESA investigators and institutions can be found at http://www.mesa-nhlbi.org.

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**Disclosures**

R. Warnick, D.M. Hoefer, and J.P. McConnell are associated with Health Diagnostic Laboratory, Inc, the clinical laboratory responsible for obtaining Lp(a) data in the present study. Joseph McConnell serves as the Chief Executive Officer, Russell Warnick serves as the Chief Scientific Officer, and Daniel Hoefer serves as the Laboratory Director. The other authors report no conflicts.

**References**

Lipoprotein(a) (Lp(a)) is a well-known lipid risk factor for coronary heart disease (CHD). Previous studies have shown that Lp(a) levels and distribution patterns vary by race; however, it remains unclear whether Lp(a) imposes risk across all races. We, therefore, aimed to examine the linear associations of Lp(a) with CHD and whether existing thresholds of 30 or 50 mg/dL identify CHD risk in black, white, Chinese American, and Hispanic Multi-Ethnic Study of Atherosclerosis (MESA) participants during a median 8.5-year follow-up period. Continuous associations of Lp(a) and CHD were only significant in black and white study participants. It was found that the 50 mg/dL cut point identifies CHD risk in 3 of the 4 races/ethnicities, but the lower 30 mg/dL cut point may be appropriate for detecting CHD risk for black individuals. Further study and development of clinical ranges are necessary to identify desirable and at-risk Lp(a) levels across individual races/ethnicities.
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**SUPPLEMENTAL MATERIAL**

Table I. Continuous Net Reclassification Improvement and c-statistics were generated to determine whether Lp(a) improves prediction of incident coronary heart disease cases and non-cases over the 8.5 year median study period. The baseline risk prediction model consisted of multiple variables including age, sex, smoking, hypertension medication, systolic blood pressure, diabetes, non-Lp(a) LDL-C, HDL-C, and log-triglycerides.

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<th></th>
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<th>1/2NRI</th>
<th>Lower CI</th>
<th>Upper CI</th>
<th>P value</th>
<th>M+</th>
<th>M-</th>
<th>Δ C-statistic</th>
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<tr>
<td><strong>30 mg/dL</strong></td>
<td>All</td>
<td>0.10</td>
<td>0.01</td>
<td>0.17</td>
<td>0.04*</td>
<td>0.42</td>
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<td>0.21</td>
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<td>All</td>
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<tr>
<td><strong>Per unit log Lp(a)</strong></td>
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<td>1.00</td>
<td>0.48</td>
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</tr>
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</table>

**M+ (Event NRI)** = the proportion of event subjects whose predicted probability of having an event in the new model is greater than that in the baseline model. A positive change in M+ represents an improvement in sensitivity.
**M- (Non-event NRI)** = the proportion of non-event subjects whose predicted probability of having an event in the new model is greater than that in the baseline model. A negative change in M- represents an improvement in specificity.
METHODS AND MATERIALS

Study Population

The design of the MESA study has been described previously [1], and information about the MESA protocol is available at www.mesa-nhlbi.org. Briefly, 6,814 men and women between the ages of 45 and 84 years without clinical evidence of cardiovascular disease were recruited from 6 communities in the U.S. Institutional Review Board approval was obtained at all MESA sites, and all participants gave informed consent.

The current study excluded participants who were taking lipid-lowering medication at baseline (visit 1) and those with missing covariates. Participants in the MESA 1000 population (a random subcohort of 1,000 MESA individuals who were selected for more extensive study) were also excluded due to limited supply of specimens. The remaining study population contains 4,593 individuals of the following races/ethnicities: Black (n=1,323), Caucasian (n=1,677), Chinese-American (n=548), and Hispanic (n=1,044). All study participants gave informed consent and were followed for a median follow-up period of 8.5 years. Age, race/ethnicity, sex, education, baseline measurements including hypertension (on hypertension medication or with systolic blood pressure > 140 mmHg), diabetes (treated or untreated diabetes mellitus as determined by 2003 American Diabetes Association fasting criteria algorithm), and smoking status (former and current) were recorded. All related laboratory measurements and imaging data were obtained at baseline as well.

Laboratory measurement

Fasting plasma triglyceride, total cholesterol, high density lipoprotein cholesterol (HDL-C) concentrations were measured as described previously [2]. Low density lipoprotein-cholesterol (LDL-C) was calculated based on the Friedewald formula in participants with
triglycerides <400 mg/dL. The calculated LDL-C includes the cholesterol contained in Lp(a) particles. To account for this overlap in the LDL-C covariate with the Lp(a) exposure variable, we subtracted Lp(a)-cholesterol (measured by gradient gel electrophoresis at Health Diagnostics Laboratory Inc., Richmond, VA) from LDL-C to get the non-Lp(a) LDL-C. Lp(a) mass concentration was measured with a latex-enhanced turbidimetric immunoassay (Denka Seiken, Tokyo, Japan). The active reagent (R2) contains a suspension of latex particles coated with anti-Lp(a) antibodies. Following incubation with serum, agglutination is detected by a change in absorbance at a wavelength of 700 nm, which is proportional to the mass, based on a five-level calibration. This assay uses an analytical approach that circumvents the problems in measuring Lp(a) [4] by using 1) multiple calibrators that control for varying apo(a) sizes (187 to >662 kDa) among individuals; and 2) isoform-insensitive antibodies that are not directed to the repeating element within apo(a), Kringle 4 type 2.

**Incident Coronary Heart Disease**

Incident CHD was defined as the first occurrence of any of the following over a median 8.5 year follow up period: myocardial infarction (n=101), resuscitated cardiac arrest (n=17), CHD death (n=45), or definite angina (n=109). Definite angina was defined as symptoms of typical chest pain and physician diagnosis of angina followed by coronary artery bypass grafting or percutaneous coronary intervention (PTCA), evidence of ischemia by stress tests or resting ECG, or ≥70% obstruction on coronary angiography. In addition, there were 51 cases of ‘probable angina,’ but only nine were included as CHD cases in the present analysis. Probable angina cases that were included showed symptoms of typical chest or atypical symptoms and physician diagnosis of angina followed by coronary artery bypass grafting. Probable angina cases followed by PTCA were excluded (n=4) when obstruction did not reach 70%. An
additional 14 individuals that did not experience angina and underwent PTCA without evidence of obstruction $\geq 70\%$ were also excluded.

**Statistical Model**

Statistical analyses were conducted using Stata (version 12.1, Stata Corp, College Station, TX) and R [3]. Baseline characteristics were presented as means (SD) for continuous variables and frequencies (%) for categorical variables. Missing data were excluded when calculating frequencies. Cox regression was used to test for association between Lp(a) and the primary outcomes of CHD, adjusting for age, sex, education, smoking, hypertension medication, systolic blood pressure, diabetes, race, and the standard lipid measures including HDL-C, non-Lp(a) LDL-C, and (log-transformed) triglycerides. Lp(a) level was first treated as a continuous, log-transformed variable; subsequent analysis treated Lp(a) as a categorical variable dichotomized by 30 mg/dL or 50 mg/dL cut points. The proportional hazards assumption was examined using Schoenfeld residuals. We further carried out subgroup analysis for each ethnic group, using the same statistical model.
REFERENCES


