Lipoprotein(a) and Increased Cardiovascular Risk in Women

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Journal Title: Clinical Cardiology

Volume: Volume 39, Number 2

Publisher: Wiley Open Access: Various Creative Commons Licenses | 2016-02-01, Pages 96-102

Type of Work: Article | Final Publisher PDF

Publisher DOI: 10.1002/clc.22500

Permanent URL: https://pid.emory.edu/ark:/25593/v0gvr

Final published version: http://dx.doi.org/10.1002/clc.22500

Clinical Investigations

PREVENTION

Lipoprotein(a) and Increased Cardiovascular Risk in Women

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ABSTRACT

Background: Approximately 20% of the population has elevated circulating levels of lipoprotein(a) (Lp[a]), one of the most robust predictors of cardiovascular disease risk. This is particularly true for women.

Hypothesis: Many female patients with "normal" traditional risk factors or low atherosclerotic cardiovascular disease (ASCVD) risk scores may harbor high risk related to elevated levels of Lp(a).

Methods: A retrospective, cross-sectional study of consecutive female patients presenting to Heart Centers for Women was performed. Discordance between low-density lipoprotein cholesterol (LDL-C) and Lp(a) was determined. The ASCVD risk and Reynolds Risk Score models A (RRS-A) and B (RRS-B) were calculated, and level of agreement in patients meeting treatment threshold (≥7.5% for ASCVD, ≥10% for RRS-A and RRS-B) were compared.

Results: Among 713 women, 290 (41%) had elevated Lp(a); however, LDL-C and Lp(a) were weakly correlated ($r = 0.08$). Significant discordance was observed between abnormal LDL-C and Lp(a) levels (McNemar $P = 0.03$). There was moderate correlation between RRS-A and ASCVD risk ($r = 0.71$, $P < 0.001$), and Bland-Altman plot showed diminished correlation with increased risk. More patients met treatment threshold by ASCVD risk estimation, but nearly 1 out of 20 patients met treatment threshold by RRS-A but not ASCVD score.

Conclusions: There is high prevalence of elevated Lp(a) among women presenting to Heart Centers for Women. Although traditional risk markers such as elevated LDL-C or high ASCVD risk may be absent in some women, elevated Lp(a) may identify patients who may benefit from aggressive risk-factor modification and pharmacologic therapy.

Introduction

Since the inception of the Framingham Heart Study more than 65 years ago, efforts have been made to accurately predict cardiovascular disease (CVD) risk for major adverse cardiac events. The field of risk prediction and CVD prevention continues to evolve with the identification of novel risk factors and biomarkers, such as lipoprotein(a) (Lp[a]). Approximately 20% of the population has elevated circulating levels of Lp(a), which is independent of age, sex, or lipid levels.[1] Studies estimate that up to 90% of the variation in plasma Lp(a) levels may be due to genetic factors, making Lp(a) the most prevalent inherited risk factor for CVD.[2] Lipoprotein(a) is recognized as an independent risk factor for coronary artery disease (CAD), stroke, peripheral arterial disease, and aortic stenosis.[3–9] Levels of Lp(a) >50 mg/dL, the 80th percentile for most populations, have shown a consistent and independent positive association with CVD risk in epidemiological studies.[10] Importantly, this increased risk has been shown to be higher for women than men.[11,12] In a prospective analysis of the Framingham study, elevated Lp(a) was shown to be a strong and independent predictor of myocardial infarction (MI) in women.[13] Despite that, Lp(a) was not incorporated in the Framingham Risk Score or any other commonly used risk-prediction tools.

In 2007, the Reynolds Risk Score models A (RRS-A) and B (RRS-B) were developed to more accurately identify women's risk of coronary revascularization, MI, coronary heart disease death, stroke, or stroke death. By adding high-sensitivity C-reactive protein, Lp(a), and family history of CAD, RRS reclassified 40% to 50% of women at intermediate

Rami Doukky serves on the advisory board for and has received research funding from Astellas Pharma.
The authors have no other funding, financial relationships, or conflicts of interest to disclose.

Clin. Cardiol. 39, 2, 96–102 (2016)
Published online in Wiley Online Library (wileyonlinelibrary.com)
DOI:10.1002/clc.22500

Received: September 8, 2015
Accepted with revision: November 18, 2015

risk based on the National Cholesterol Education Program Adult Treatment Panel III guidelines into higher or lower risk categories.[14] Though the RRS used Lp(a) in the best-fitting model, Model A, it was omitted from their simplified clinical model, Model B, to allow for wider clinical application, leaving Lp(a) out of risk calculation.[14]

In 2013, the American College of Cardiology Foundation/American Heart Association, in an effort to focus more on atherosclerotic cardiovascular disease (ASCVD) risk and less on cholesterol-level goals, published new cholesterol guidelines and recommendations for cholesterol and CVD risk management.[15] Lifestyle modification was strongly recommended for all patients, and statin therapy was also recommended for patients with a 10-year risk for major adverse cardiac events of ≥7.5%, markedly elevated low-density lipoprotein cholesterol (LDL-C), patients with known CVD, or patients age 40 to 75 years with diabetes mellitus.[15,16] In the era of focusing on CVD risk prediction and disease prevention, Lp(a) may prove to be an important risk marker, especially in women, that can guide treatment decisions.

In an effort to improve cardiac outcomes in women, we studied female patients presenting to the Rush University and Emory University Heart Centers for Women who had Lp(a) levels to determine (1) the incidence of elevated and extreme Lp(a) levels, and (2) the agreement in treatment thresholds for RRS-A and both RRS-B and ASCVD scores. We hypothesized that female patients with "normal" traditional risk factors or low ASCVD risk scores harbor unidentified CVD risk due to high-risk levels of Lp(a).

Methods

A retrospective, cross-sectional study was conducted among consecutive adult female patients presenting to Rush University and Emory University Heart Centers for Women from 2006 to 2014 who had Lp(a) determination. The following data were determined by chart review: age, total cholesterol, LDL-C, high-density lipoprotein cholesterol (HDL-C), apolipoprotein B (ApoB), Lp(a), high-sensitivity C-reactive protein, current smoking status, family history of CAD, hypertension, and hypertension treatment.

Measurement of Lipoproteins

Lipoprotein concentrations were measured in a blinded manner at Quest Diagnostics Nichols Institute (San Juan Capistrano, CA) using commercially available assays. Serum was collected and transported refrigerated to the laboratory. The LDL-C, HDL-C, and triglycerides were measured by spectrophotometry. Non-HDL cholesterol (NHDL-C) was calculated. Lipoprotein(a) was measured with immunoturbidimetric assay. Lipoprotein(a) was measured and reported in nmol/L to reflect the concentration of Lp(a) particles and thus avoid the effect of the number of Kringle IV type-2 repeats on molecular weight. Conversion to mg/dL was approximated by dividing nmol/L values by 2.15 ($r^2 = 0.998$ for linearity).[4]

From the study sample, abnormal lipid thresholds were determined a priori as follows: NHDL-C, 127 mg/dL; LDL-C, 106 mg/dL; ApoB, 82 mg/dL; Lp(a), 30 mg/dL. Unidentified, increased risk was determined by identifying discordance between abnormal LDL-C level and abnormal levels of NHDL-C, ApoB, and Lp(a). Women on lipid-lowering therapy were not excluded from analysis.

Measurement of Risk Estimates

Ten-year risk estimates according to RRS-A and RRS-B were calculated. Similarly, 10-year ASCVD risk estimates were calculated and patients were classified as either low-risk (<7.5%) or high-risk (≥7.5%). Treatment thresholds for both RRS-A and RRS-B and ASCVD were ≥10% and ≥7.5%, respectively.[14,15] Agreement in treatment thresholds was compared for RRS-A and both ASCVD and RRS-B. We opted to compare treatment threshold instead of absolute 10-year risk, as ASCVD risk includes MI, coronary heart disease death, stroke, and stroke death, whereas RRS-A and RRS-B include these endpoints, as well as coronary revascularization.

Statistical Analysis

Continuous data are presented as mean ± SD. The McNemar test was used to compare paired dichotomous data, which were presented as numbers (percentages). Correlations were illustrated visually using scatter plots that were split into quadrants based on abnormal thresholds. The 80th, 85th, 90th, and 95th percentiles of Lp(a) were determined for the study population, and proportions at or above each percentile were tabulated. Pearson linear correlation coefficients (r) and corresponding P values were calculated to determine correlation between LDL-C and levels of NHDL-C, ApoB, and Lp(a). Similarly, Pearson linear correlation coefficients and corresponding P values were calculated to assess correlation between 10-year risk estimates of ASCVD and each RRS-A and RRS-B, and RRS-B and RRS-A. Bland-Altman plots were used to evaluate source of discordance between these risk scores. Cohen's κ agreement coefficient and corresponding P value were calculated to determine the degree and significance of agreement between treatment thresholds. R Language and Environment for Statistical Computing, version 3.1.3 (R Foundation, Vienna, Austria) was used for all statistical analyses. Two-tailed P values < 0.05 were considered statistically significant.

Investigations were conducted in accordance with the Declaration of Helsinki. This study received approval by the institutional review board at each collaborating institution.

Results

We identified 713 consecutive women with a mean age of 60.5 ± 8.8 years (range, 18–83 years) who had Lp(a) level determination. Table 1 presents the baseline characteristics and demographics of the study population. Notably, this population is composed of predominantly Caucasian (74.7%) and overweight women. The second most represented race was African Americans (15.9%). Approximately 50% of the population carried a diagnosis of hypertension (HTN).

As presented in Table 2, 290 (41.0%) patients had Lp(a) levels ≥30 mg/dL, whereas 142, 108, 73, and 36 had levels ≥80th (67 mg/dL), 85th (84 mg/dL), 90th (100 mg/dL), and 95th (123 mg/dL) percentiles, respectively. Figure 1

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DOI:10.1002/clc.22500

Table 1. Baseline Characteristics

Variable	Value
Age, y	60.5 ± 8.8
BMI, kg/m²	28.2 ± 6.6
SBP, mm Hg	122.0 ± 16.0
Ethnicity	
Asian	8 (1.2)
Black	105 (15.9)
White	493 (74.7)
Hispanic	26 (3.9)
Other	18 (2.7)
Unanswered	10 (1.5)
HTN	317 (48)
HTN treatment	303 (45.9)
DM	48 (7.3)
Smoking	69 (10.5)
Family history of CAD	187 (28.3)
Lipids, mg/dL	
TC	192.6 ± 37.5
LDL-C	107.2 ± 36.0
HDL-C	65.3 ± 18.2
TG	103.9 ± 62.6
ApoB	82.0 ± 20.1
Lp(a)	38.4 ± 41.2
hs-CRP, mg/L	3.2 ± 5.6

Abbreviations: ApoB, apolipoprotein B; BMI, body mass index; CAD, coronary artery disease; DM, diabetes mellitus; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; HTN, hypertension; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); SBP, systolic blood pressure; SD, standard deviation; TC, total cholesterol; TG, triglycerides.
Data are presented as n (%) or mean ± SD.

Table 2. Prevalence of Elevated Lp(a) Levels

Reference Level	Lp(a) Level	N (%)
Abnormal level	≥30 mg/dL	290 (41)
≥80th percentile	≥67 mg/dL	142 (20)
≥85th percentile	≥84 mg/dL	108 (15)
≥90th percentile	≥100 mg/dL	73 (10)
≥95th percentile	≥122.7 mg/dL	36 (5)

Abbreviations: Lp(a), lipoprotein(a).

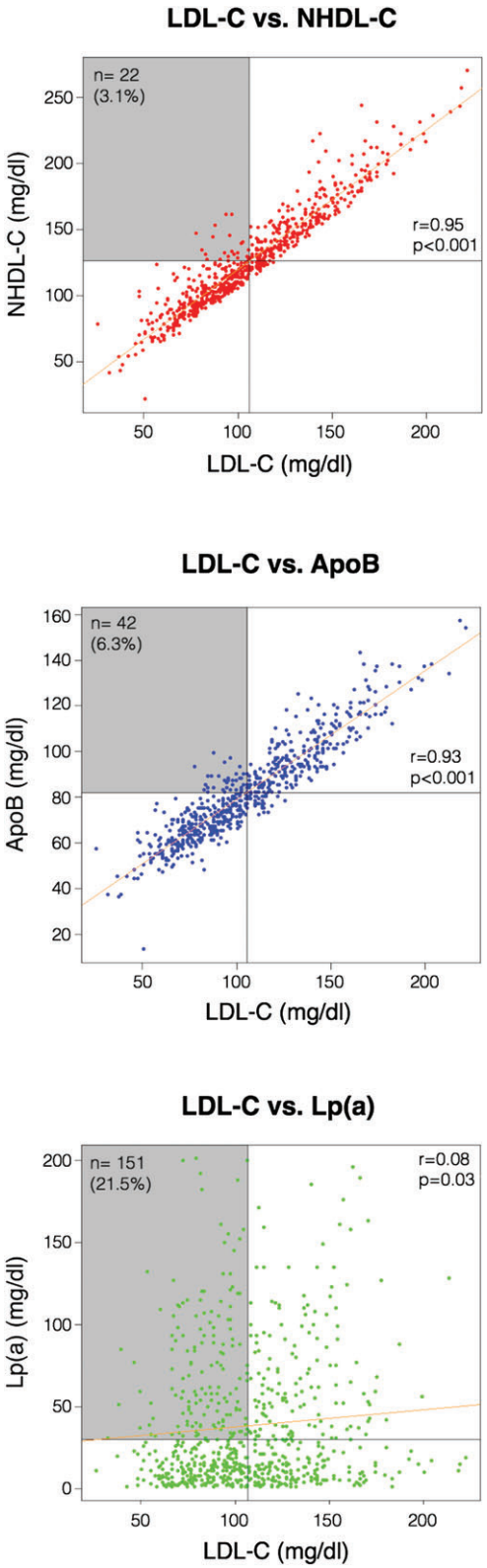

Figure 1. Correlation plots for LDL-C and ApoB, NHDL-C, and Lp(a). There were strong correlations and minimal discordance between LDL-C and ApoB and between LDL-C and NHDL-C. There was a weak correlation and significant discordance seen with LDL-C and Lp(a). Abbreviations: ApoB, apolipoprotein B; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); NHDL-C, non–high-density lipoprotein cholesterol.

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DOI:10.1002/clc.22500

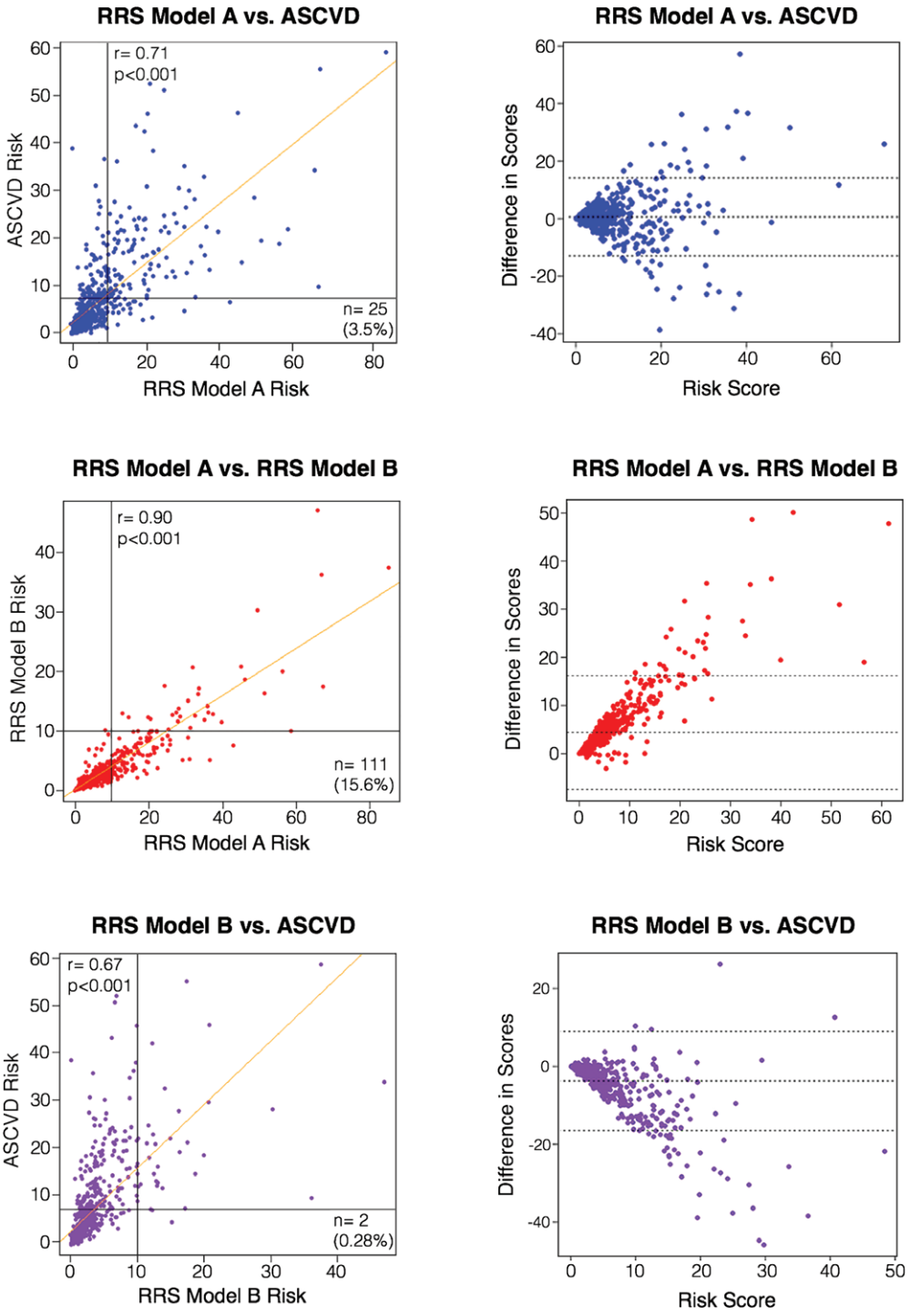

Figure 2. Correlation and Bland-Altman comparing ASCVD score and RRS. Bland-Altman plot of ASCVD scores and RRS-A and RRS-B showing agreement in low-risk levels and agreement divergence at high-risk levels. Abbreviations: ASCVD, atherosclerotic cardiovascular disease; RRS-A, Reynolds Risk Score model A; RRS-B, Reynolds Risk Score model B.

illustrates a strong correlation between LDL-C and ApoB ($r = 0.93$, $P < 0.001$), and only 6.3% of women had discordantly high ApoB but normal LDL-C. Similarly, there was a strong correlation between LDL-C and NHDL-C ($r = 0.95$, $P < 0.001$), and only 3.1% of women had discordantly high NHDL-C but normal LDL-C. However, the correlation between LDL-C and Lp(a) was weak ($r = 0.08$, $P = 0.03$), and 21.5% of women had discordantly high Lp(a) but normal LDL-C.

Figure 2 shows a moderate correlation between ASCVD score and RRS-A ($r = 0.71$, $P < 0.001$). Similarly, there was moderate correlation between ASCVD score and

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DOI:10.1002/clc.22500

Table 3. Comparison of Treatment Threshold for RRS-A and Both ASCVD and RRS-B

		ASCVD Treatment		RRS-B Treatment	
		Yes, 203 (28.5)	No, 510 (71.5)	Yes, 34 (4.8)	No, 679 (95.2)
RRS-A treatment	Yes, 144 (20.2)	119 (58.6)	25 (4.9)	33 (97.1)	111 (16.3)
	No, 569 (79.8)	84 (41.4)	485 (95.1)	1 (2.9)	568 (83.7)

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; RRS-A, Reynolds Risk Score, Model A; RRS-B, Reynolds Risk Score, Model B.
Data are presented as n (%).

RRS-B ($r = 0.67$, $P < 0.001$). The correlation between RRS-A and RRS-B, however, was excellent ($r = 0.90$, $P < 0.001$). Bland-Altman plots demonstrated good correlation between ASCVD and each of RRS-A and RRS-B, but correlation diminished with increasing risk (Figure 2).

The proportion of women meeting treatment threshold using RRS-A and ASCVD scores were significantly different (McNemar $P < 0.001$; Table 3). Analyzing treatment thresholds, there were more patients meeting treatment threshold by ASCVD score (n = 203, 28.5%) compared with RRS-A (n = 144, 20.2%) ($\kappa = 0.589$, $P < 0.001$). Twenty-five women (4.9%) who met treatment threshold by RRS-A did not meet threshold by ASCVD score. The proportion of patients meeting treatment threshold using the RRS-A and RRS-B scores were significantly different (McNemar $P < 0.001$) and the agreement in meeting treatment threshold was relatively modest ($\kappa = 0.318$, $P < 0.001$). Only 34 women (4.8%) met treatment threshold by RRS-B compared with 144 (20.2%) by RRS-A, whereas only 1 patient was identified for treatment by RRS-B and not by RRS-A.

Discussion

In this study, we found that approximately 40% of women presenting to Heart Centers for Women had elevated Lp(a). This proportion is much higher than the 20% reported in the general population and may put these patients at increased risk for CVD events. With a greater focus now on overall CVD risk, Lp(a) deserves attention, especially in women. Although patients with low LDL-C are typically considered to be low risk, their elevated Lp(a) imparts increased risk. It should be noted that treatment thresholds for both ASCVD and RRS models A and B were used as surrogates for outcomes, not CV events. The study suggests that ASCVD risk scores may accurately identify patient populations that benefit from pharmacologic therapy, especially older patients; however, those with elevated Lp(a) would not have been identified if left unchecked. Patients categorized as low risk by ASCVD risk, and thus not meeting treatment threshold, may meet treatment threshold by RRS-A when Lp(a) is used in calculating risk. As illustrated in this study, more patients met criteria for cholesterol treatment by ASCVD risk compared with RRS-A and RRS-B, which is largely driven by the declining cost of high-potency statin drugs and relatively low side-effect profile, making statins tolerable and inexpensive therapy. Additionally, nearly 1 in 20 patients who met treatment threshold by RRS-A did not meet threshold by ASCVD score. The addition of Lp(a) to risk tools in the future may capture even more patients not identified by ASCVD risk who would benefit from aggressive risk-factor and lifestyle modification and high-intensity statin therapy to decrease overall CVD risk.

To our knowledge, this is the first study to demonstrate the frequency of elevated Lp(a) in women who present to a Heart Center for Women with symptoms or who desire a heart-health evaluation and is the first study to evaluate the usefulness of Lp(a) in a clinical setting.

Although prior studies have shown inconsistent data on the effect of statin therapy in patients with elevated Lp(a), the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial,[4] a primary prevention trial using rosuvastatin, showed Lp(a) was a significant determinant of risk, and treatment with rosuvastatin showed similar risk reduction in patients with high as well as low Lp(a). Recent investigations have determined that Lp(a) is a significant predictor for major adverse cardiac events, especially in intermediate-risk subjects.[17,18] A 2012 meta-analysis of 24 prospective studies with a total of 134 000 participants also showed that the addition of Lp(a) to prognostic models containing traditional risk factors produced a modest but statistically significant improvement in risk discrimination.[19] Furthermore, a prospective population study of 8720 participants that focused on extreme Lp(a) levels (≥80th percentile or >47 mg/dL) showed that the use of Lp(a) resulted in 100% correct net risk reclassification of all patients who experienced CV events over 10 years using the net reclassification index and integrated discrimination improvement.[7]

Determining Lp(a) in a clinical setting remains controversial, as many organizations and investigators do not support it.[15,20,21] However, the National Lipid Association published a consensus statement recommending screening of moderate- to high-risk patients to identify those with elevated plasma Lp(a) concentrations.[22] In addition, the European Atherosclerosis Society Consensus Panel recommends screening for elevated Lp(a) in those at intermediate or high CVD risk, a desirable level <50 mg/dL as a function of global CVD risk, and use of niacin for Lp(a) and CVD risk reduction.[10] This recommendation was prior to publication of the Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides: Impact on Global Health (AIM-HIGH) study, which showed no benefit in lowering Lp(a).[23] Others have suggested that, given the strong genetic component of Lp(a), individuals with a strong family history of premature CVD may be good candidates for screening if they do not have other risk factors.[1]

Because Lp(a) is not only atherogenic but potentially prothrombotic, its treatment may need to be targeted at both processes. Aspirin therapy (81 mg/d) has been found to

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DOI:10.1002/clc.22500

lower Lp(a) levels by approximately 20%.[24] In the Women's Health Study, carriers of an apolipoprotein(a) rs3798220 variant were associated with higher Lp(a) concentrations and double the CV risk and appeared to benefit more from aspirin than did noncarriers.[25]

From the atherogenic standpoint, the treatment of elevated Lp(a) remains controversial because no studies have been conducted to treat Lp(a) as a target. Of note, 2 major studies looked at therapy that lowered Lp(a) but had mixed outcome results. In the Heart and Estrogen-Progestin Replacement Study (HERS), Lp(a) was found to be an independent risk factor for recurrent CVD in postmenopausal women. Treatment with estrogen and progestin lowered Lp(a) levels and had a more favorable effect (relative to placebo) in women with high initial Lp(a) levels (>25.3 mg/dL) than in women with low levels. Women with elevated Lp(a) had CV benefits from the hormone-replacement therapy after the second year of treatment. In all quartiles of Lp(a), the average LDL-C was >140 mg/dL.[22,26] In contrast, the AIM-HIGH study used niacin, in addition to statins, to further reduce major adverse cardiac events and subsequently lowered Lp(a) levels, but no outcome benefit was seen. In this patient population, LDL-C was much lower than in HERS, averaging 70 mg/dL.[26] Other studies have shown such interaction with age, LDL-C, and Lp(a).[27]

Further studies addressing CVD risk are needed in women with elevated Lp(a), especially in those who smoke or use exogenous estrogen, which are all known to increase risk of thromboembolism. Trials on younger women using hormone therapy may further shed light on the interaction of Lp(a), LDL-C, and hormone therapy. A recent meta-analysis looking at oral tibolone (steroid with estrogenic, androgenic, and progestogenic properties) treatment significantly reduced circulating Lp(a) levels by 25% in postmenopausal women.[28]

Recent reviews of the pathophysiology of elevated Lp(a) underscore its complexity. It has now been found that its atherogenic and thrombotic effects can also be influenced by genes, inflammation, and other lipids. Patients with elevated Lp(a) may have different manifestations of CVD, and further studies will be needed to elucidate how patients, especially women, can benefit from detecting and managing elevated levels of Lp(a). Until guidelines from national organizations make recommendations about determining and treating elevated Lp(a), clinicians can determine which patients should have it evaluated.

Study Limitations

Limitations of this study include its retrospective nature and the absence of major adverse cardiovascular and outcomes events.

Conclusion

Women who present to cardiologists in Heart Centers for Women are at higher risk than the general population. Determination of Lp(a) in women may help better stratify women regarding their CV risk. Randomized controlled trials investigating Lp(a) treatment and interactions with other risk factors are much needed to help guide therapy in further reducing cardiovascular risk in women.

Acknowledgments

The authors acknowledge Li Shien Low, Marcel Gout, Nicole Pohlman, Ben Gastevich, and Rasa Kazlauskaite, MD for their assistance with data collection, risk calculation, and statistics.

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DOI:10.1002/clc.22500