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The association of lipoprotein(a) with incident heart failure hospitalization: Atherosclerosis Risk in Communities study

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ABSTRACT

Background and aims: Lipoprotein(a) [Lp(a)] is a proatherogenic lipoprotein associated with coronary heart disease, ischemic stroke, and more recently aortic stenosis and heart failure (HF). We examined the association of Lp(a) levels with incident HF hospitalization in the Atherosclerosis Risk in Communities (ARIC) study. We also assessed the relationship between Lp(a) levels and arterial stiffness as a potential mechanism for development of HF.

Methods: Lp(a) was measured in 14,154 ARIC participants without prevalent HF at ARIC visit 1 (1987–1989). The association of Lp(a) quintiles with incident HF hospitalization was assessed using Cox proportional-hazards models. Arterial stiffness parameters were stratified based on Lp(a) quintiles, and *p*-trend was calculated across ordered groups.

Results: At a median follow-up of 23.4 years, there were 2605 incident HF hospitalizations. Lp(a) levels were directly associated with incident HF hospitalization in models adjusted for age, race, gender, systolic blood pressure, history of hypertension, diabetes, smoking status, body mass index, heart rate, and high-density lipoprotein cholesterol (quintile 5 *vs.* quintile 1: hazard ratio [HR] 1.24, 95% confidence interval [CI] 1.09–1.41; *p*-trend across increasing quintiles <0.01), but not after excluding prevalent and incident myocardial infarction cases (HR 1.07, 95% CI 0.91–1.27; *p*-trend = 0.70). When adjusted for age, gender, and race, Lp(a) quintiles were not significantly associated with arterial stiffness parameters.

Conclusions: Increased Lp(a) levels were associated with increased risk of incident HF hospitalization. After excluding prevalent and incident myocardial infarction, the association was no longer significant. Lp(a) levels were not associated with arterial stiffness parameters.

1. Introduction

Lipoprotein (a) [Lp(a)] is a proatherogenic lipoprotein composed of a low-density lipoprotein (LDL)–like moiety with a unique glycoprotein, apolipoprotein (a) [apo(a)], which is covalently linked to a single molecule of apolipoprotein B-100 (apoB-100) of the LDL moiety. Elevated plasma levels of Lp(a) are a significant risk factor

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for atherosclerotic cardiovascular disease [1–6]. We have previously shown that high levels of Lp(a) are significantly associated with an increased risk for coronary heart disease (CHD) and stroke in the Atherosclerosis Risk in Communities (ARIC) cohort [1,7].

Elevated levels of Lp(a) may be associated with higher risk of heart failure for several reasons. Given its atherothrombotic properties, Lp(a) may increase the risk for heart failure after ischemic myocardial injury. Additionally, Lp(a) has been implicated in the development of aortic valve stenosis [8–12], a phenomenon thought to be related to valvular calcification and stiffness, which also contribute to the development of heart failure [13]. Furthermore, through enhanced atherosclerosis, Lp(a) may increase arterial stiffness, which could also augment heart failure risk [14].

To our knowledge, only one study has assessed the relationship between Lp(a) levels and risk for heart failure [15]. In addition, no published study has examined the relationships among Lp(a) levels, arterial stiffness, and heart failure. We hypothesized that higher levels of Lp(a) would be associated with greater risk for incident heart failure hospitalization. We also postulated that increased Lp(a) levels would be associated with increased arterial stiffness and subsequent incident heart failure hospitalization. Therefore, the purpose of this study is to examine the association of Lp(a) levels with incident heart failure hospitalization and arterial stiffness in the ARIC study.

2. Patients and methods

2.1. Study participants

The ARIC study is a prospective study of cardiovascular disease incidence in 15,792 men and women between the ages of 45 and 64, who were recruited from four US communities (Minneapolis, Minnesota; Washington County, Maryland; Forsyth County, North Carolina; Jackson, Mississippi) in 1987–1989. Additional description of the ARIC study design has been published elsewhere [16]. At ARIC visit 1 (1987–1989), 752 participants had a preexisting diagnosis of heart failure. We excluded those without data on Lp(a), incident heart failure hospitalization, or covariates (n = 1535). We also excluded race other than African American or White (n = 48) and African Americans from Minnesota and Washington County field centers (n = 55), as these cohorts have numbers that are too small for adequate statistical adjustment. This resulted in a total of 14,154 participants who were included in our analysis of Lp(a) and incident heart failure hospitalization (Supplemental Fig. 1). Arterial stiffness parameters from ARIC visit 2 (1990–1992) were available in 9523 participants, in whom we assessed associations of Lp(a) with arterial stiffness parameters and heart failure.

The apo(a) component of Lp(a) may contain a variable number of kringle IV type 2 repeats that can affect characteristics such as isoform size and plasma Lp(a) levels [17,18]. ARIC investigators measured Lp(a) at ARIC visit 1 with a kringle IV type 2 repeat–sensitive assay [19] for analysis of Lp(a) and incident heart failure hospitalization. We performed confirmatory analyses with Lp(a) values measured a decade later at visit 4 (1996–1998) using a kringle IV type 2 repeat–insensitive assay [20]. Participants with prevalent heart failure at visit 4 were excluded.

2.2. Outcomes and covariates

Incident heart failure hospitalization was defined by *International Statistical Classification of Diseases and Related Health Problems* (ICD) codes of 428. x (9th Revision) or I50 (10th Revision) in any position on the hospital discharge list or on a death certificate with death from heart failure in any position [21]. CHD events are defined as definite or probable MI, fatal CHD, or cardiac procedure.

Cigarette smoking and the use of antihypertensive and lipid-lowering medications were obtained from a standardized questionnaire. Hypertension was defined as systolic blood pressure ≥140 mm Hg and diastolic blood pressure ≥90 mmHg, or the use of antihypertensive medications during the previous 2 weeks. Diabetes was defined as a fasting plasma glucose level ≥126 mg/dL, a nonfasting plasma glucose level ≥200 mg/dL, or a self-reported history of physician-diagnosed diabetes or treatment for diabetes.

2.3. Lipids and lipoproteins

Lipid measurements were performed on 12-h fasting plasma samples that were stored at −70 °C with ethylenediaminetetraacetic (EDTA) acid as the anticoagulant. Plasma total cholesterol, high-density lipoprotein cholesterol (HDL-C), and triglycerides were measured using enzymatic methods [22]. LDL cholesterol (LDL-C) was calculated using the Friedewald equation [23]. At visit 1, Lp(a) was measured using a double-antibody enzyme-linked immunosorbent assay technique as previously described [19] and at visit 4 using a commercially available automated immunoturbidimetric assay (Denka Seiken Co. Ltd., Tokyo, Japan) [20]. Lp(a) values at visit 1 were standardized using a conversion equation derived from a comparison between samples at visit 1 measured by both assays in 100 samples from an entire Lp(a) distribution with equal representation from both genders and ethnic groups, and there was excellent correlation (Pearson $r = 0.88$) without evidence of systematic bias at high or low Lp(a) levels, as previously described [1].

2.4. Ultrasound imaging and determination of arterial wall parameters

At ARIC visit 2, participants were asked to refrain from smoking, vigorous exercise, and caffeine the night prior to ultrasound imaging. Methods for the acquisition of electrocardiography-gated B-mode ultrasound images and for echo tracking of arterial diameter in the ARIC study have been described previously [16,24–26]. Arterial wall characteristics were determined by measuring arterial diameter changes over the cardiac cycle for an average of 5.6 cardiac cycles. Arterial wall characteristics were derived from ultrasound measurements as well as from supine brachial blood pressure measured at ARIC visit 2. The arterial wall parameters used in the current study include pressure-strain modulus, carotid arterial strain, arterial distensibility, arterial compliance, and stiffness index [24–26], and equations used to calculate these indices are shown in Supplemental Table 1. Higher pressure-strain modulus and stiffness index and lower carotid arterial strain, arterial distensibility, and compliance suggest increased arterial stiffness [25].

2.5. Statistical analysis

In the current analysis, we examined the association between Lp(a) levels from ARIC visit 1 and incident heart failure hospitalization. Characteristics were compared by Lp(a) levels at baseline (ARIC visit 1) using chi-squared test for categorical variables and Student's t-test or Kruskal–Wallis rank test for continuous variables as appropriate. The *p*-trend tests a linear increase in log relative hazard with increasing quintiles. Participants were followed up for incident heart failure hospitalization or until loss to follow-up, death, or December 31, 2012 (whichever came first). We used multivariable Cox proportional-hazards regression models to investigate the association between visit 1 Lp(a) levels and incident heart failure hospitalization. Lp(a) level was treated as a categorical variable by quintiles. The lowest quintile was considered as the