HHS Public Access

Author manuscript

J Am Coll Cardiol. Author manuscript; available in PMC 2025 January 14.

Published in final edited form as:

J Am Coll Cardiol. 2023 December 12; 82(24): 2280–2291. doi:10.1016/j.jacc.2023.10.016.

Association of Lipoprotein(a) Levels With Myocardial Fibrosis in the Multi-Ethnic Study of Atherosclerosis

Omar Chehab, MD, MS[a], **Ashkan Abdollahi, MD**[a], **Seamus P. Whelton, MD, MPH**[a], **Colin O. Wu, PHD**[b], **Bharath Ambale-Venkatesh, PHD**[c], **Wendy S. Post, MD, MS**[a], **David A. Bluemke, MD**[d], **Michael Y. Tsai, PHD**[e], **João A.C. Lima, MD, MBA**[a,c]

[a]Division of Cardiology, Department of Medicine, Johns Hopkins University, Baltimore, Maryland, USA

[b]Office of Biostatistics Research, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland, USA

[c]Department of Radiology, Johns Hopkins University, Baltimore, Maryland, USA

[d]Department of Radiology, University of Wisconsin School of Medicine and Public Heath, Madison, Wisconsin, USA

[e]Department of Pathology, University of Minnesota, Saint Paul-Minneapolis, Minneapolis, Minnesota, USA

Abstract

BACKGROUND—Lipoprotein(a) (Lp[a]) has been identified as an emerging risk factor for adverse cardiovascular (CV) outcomes, including heart failure. However, the connections among Lp(a), myocardial fibrosis (interstitial and replacement), and cardiac remodeling as pathways to CV diseases remains unclear.

OBJECTIVES—This study investigated the relationship between Lp(a) levels and myocardial fibrosis by cardiac magnetic resonance (CMR) T1 mapping and late gadolinium enhancement, as well as cardiac remodeling by cine CMR, in the MESA (Multi-Ethnic Study of Atherosclerosis) cohort.

METHODS—The study included 2,040 participants with baseline Lp(a) measurements and T1 mapping for interstitial myocardial fibrosis (IMF) evaluation in 2010. Lp(a) was analyzed as a continuous variable (per log unit) and using clinical cutoff values of 30 and 50 mg/dL. Multivariate linear and logistic regression were used to assess the associations of Lp(a) with CMR measures of extracellular volume (ECV fraction [ECV%]), native T1 time, and myocardial scar, as well as parameters of cardiac remodeling, in 2,826 participants.

ADDRESS FOR CORRESPONDENCE: Dr João A.C. Lima, Division of Cardiology, Johns Hopkins University, 600 North Wolfe Street, Baltimore, Maryland 21287-0409, USA. jlima@jhmi.edu.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

APPENDIX For supplemental tables, please see the online version of this paper.

RESULTS—Higher Lp(a) levels were associated with increased ECV% (per log-unit Lp[a]; β = 0.2%; $P = 0.007$) and native T1 time (per log-unit Lp[a]; β = 4%; $P < 0.001$). Similar relationships were observed between elevated Lp(a) levels and a higher risk of clinically significant IMF defined by prognostic thresholds per log-unit Lp(a) of ECV% (OR: 1.20; 95% CI: 1.04–1.43) and native T1 (OR: 1.2; 95% CI: 1.1–1.4) equal to 30% and 955 ms, respectively. Clinically used Lp(a) cutoffs (30 and 50 mg/dL) were associated with greater prevalence of myocardial scar (OR: 1.85; 95% CI: 1.1–3.2 and OR: 1.9; 95% CI: 1.1–3.4, respectively). Finally, higher Lp(a) levels were associated with left atrial enlargement and dysfunction.

CONCLUSIONS—Elevated Lp(a) levels are linked to greater subclinical IMF, increased myocardial scar prevalence, and left atrial remodeling.

Keywords

cardiac magnetic resonance; interstitial myocardial fibrosis; lipoprotein(a); magnetic resonance imaging; myocardial scar; T1 mapping

Myocardial fibrosis, characterized by the accumulation of extracellular matrix (ECM) proteins and collagen in the myocardium, is a key process underlying cardiac remodeling and progression to clinically manifested cardiovascular diseases (CVDs), including atrial fibrillation and heart failure.[1] Population-based studies, such as MESA (Multi-Ethnic Study of Atherosclerosis) and the UK Biobank, have linked increased myocardial fibrosis measured by cardiac magnetic resonance (CMR) to worse cardiovascular (CV) events and outcomes.[2,3] Indeed, both interstitial and replacement fibrosis, 2 distinct pathways of myocardial fibrogenesis, contribute to cardiac dysfunction, heart failure, and arrhythmias.[1,4] Reactive interstitial fibrosis, associated with traditional CV risk factors such as pressure overload, microvascular disease, and aging, involves ECM expansion within the myocardium.[1] Replacement fibrosis, conversely, substitutes healthy myocardium with fibrotic tissue after injury by ischemic infarction or inflammation. Untreated reactive interstitial fibrosis may also lead to irreversible replacement fibrosis.[1]

Identifying modifiable risk factors for myocardial fibrosis is essential for developing targeted prevention and treatment strategies to improve CV health because effective treatments for patients with heart failure with preserved ejection fraction (HFpEF) are still lacking.[5] Approximately one-third of the general population has elevated lipoprotein(a) (Lp[a]) levels, a low-density lipoprotein (LDL)–like particle containing apolipoprotein(a) bound to apolipoprotein B-100.[6] Recent and increasing evidence has linked higher Lp(a) levels to a greater risk of coronary artery disease and cardiac-related mortality, as well as worsening aortic stenosis and heart failure.[6,7] Inflammation-related factors are associated with myocardial fibrosis progression.[8] Although Lp(a) is a prothrombotic and proinflammatory risk factor, its relationship with both interstitial and replacement myocardial fibrosis remains unclear at the population level. At present, no proven therapies exist for preventing CVD by lowering Lp(a), but the development of such therapies is being pursued on multiple fronts.[9] Understanding the relationship between Lp(a) and myocardial fibrosis is crucial to elucidating underlying mechanisms and potential therapeutic targets in CV medicine, given the strong connection of Lp(a) with CVD.

This study aimed to investigate the associations of increased Lp(a) levels with greater interstitial and replacement myocardial fibrosis, as well as adverse cardiac remodeling in a population-based cohort, by using MESA findings. We hypothesized that elevated Lp(a) levels correlate with increased markers of subclinical interstitial (extracellular volume fraction [ECV%] and native T1 time) and replacement myocardial fibrosis (using late gadolinium enhancement [LGE]) as pathways to adverse cardiac remodeling and clinically manifested CVD.

METHODS

STUDY GROUP.

The MESA study was established to explore the incidence and risk factors of CVD in individuals who initially did not exhibit any noticeable clinical CVD, cancer treated with radiation or chemotherapy, severe major illness, or cognitive impairment, as assessed by the screening interviewer at the visit 1 baseline examination.[10] Between 2000 and 2002, 6,814 men and women 45 to 84 years old, self-identified as originating from White, Black, Hispanic, or Chinese racial or ethnic backgrounds, were enrolled from 6 different U.S. locations: Baltimore, Maryland; Chicago, Illinois; Forsyth County, North Carolina; Los Angeles County, California; New York, New York; and Saint Paul, Minnesota. Ethics committees at all involved centers approved the research, and all participants gave their informed consent. More information about the study's methodology can be accessed online through the MESA website.[11] In the present study, we examined participants who were part of the MESA visit 5, conducted between 2010 and 2012. All participants underwent CMR at visit 5 and had baseline Lp(a) measurements at visit 1. In the entire cohort at visit 5 with complete CMR data (n = 2,826), including cine CMR and CMR tagging, 2,040 participants had available native T1 time data, whereas 1,262 had both extracellular volume (ECV) and myocardial scar assessments (LGE). To explore the relationship between Lp(a) and cardiac structure and function, we analyzed the entire MESA cohort at visit 5 with complete CMR data (n = 2,826).

LP(a) DETERMINATION.

After fasting, blood samples were collected, and tubes containing EDTA anticoagulant were managed according to uniform methodology.[12] These samples were divided and kept at −70 °C until the time of analyte assessment. Previously established methods were used to measure fasting triglyceride, total cholesterol, and high-density lipoprotein (HDL) cholesterol levels.[13] As the exposure variable, Lp(a) mass concentrations were assessed at baseline for 6,700 MESA samples by Health Diagnostics Laboratory using a latex-enhanced turbidimetric immunoassay (Denka Seiken) that compensates for the diverse sizes of apolipoprotein(a).[14] Total imprecision amounted to <5%.

CMR MEASUREMENT.

The previously described CMR protocol for evaluating myocardial fibrosis in the visit 5 MESA examination (2010–2012) included participants with adequate glomerular filtration rate and no history of allergic reactions to contrast agents.[15] Using 1.5-T scanners, left ventricular (LV) structure and function were assessed using steady-state free precession

sequences for LV cine imaging. Parameters included LV mass, end-diastolic volume, end-systolic volume, mass-to-volume ratio, stroke volume, and ejection fraction. CMR studies used myocardial T1 mapping to quantify interstitial fibrosis and CMR tagging to measure myocardial strain. The modified Look-Locker inversion recovery (MOLLI) sequence was performed before and after gadolinium-diethylene triamine penta-acetic acid injection, with uniform scanning parameters across all centers. T1 mapping indices included precontrast (native) and postcontrast T1 times, as well as ECV% evaluated using a single-breath-hold modified Look-Locker inversion recovery sequence.[15] Native T1 time and synthetic ECV were used as reference markers for estimating diffuse interstitial myocardial fibrosis (IMF). An increased ECV% and T1 time reflected greater IMF magnitude. Myocardial scar (replacement myocardial fibrosis) was assessed as localized LGE in either 2 adjacent short-axis slices or 1 short-axis and 1 long-axis image from the same myocardial location by using QMass version 7.2 (Medis). “Typical” ischemic scars were those involving the subendocardium within a coronary artery distribution, whereas “atypical” nonischemic scars mainly affected the midwall or subepicardium and were not associated with a specific coronary artery distribution. Additional parameters used as remodeling outcomes included left atrial (LA) volumes and function. LA and LV functional and strain parameters were calculated as detailed in previous reports.[16,17]

STATISTICAL ANALYSIS.

Continuous variables were presented as mean ± SD or median (Q1-Q3) on the basis of data normality, whereas categorical variables were expressed as frequencies and percentages. Given that Lp(a) follows a nonparametric distribution, Lp(a) measures were log-transformed in our analyses. Missing data were excluded when calculating frequencies. For a comprehensive evaluation of Lp(a) as a marker for CV risk, our approach involved assessing it as both a continuous variable through log-transformation and a categorical variable using established thresholds. Clinical guidelines from the United States and Europe recommend differing Lp(a) threshold levels (30 and 50 mg/dL, respectively), and our analysis took both into account, as well as classifying Lp(a) levels into quartiles.

Multivariate linear regression was used to evaluate the strength of associations between Lp(a) and each of the T1 mapping indices (ECV and native T1), as well as minimal LA indexed volume, LA emptying fraction, and LV circumferential strain from CMR tagging. Additionally, multivariate logistic regression was used to investigate the associations of Lp(a) with clinical cutoff points for adverse CV outcomes: ≥30% for ECV and ≥955 ms for native T1 time, as emphasized by Marques et al.[2] In a similar fashion, multivariate logistic regression was applied to examine the correlation between Lp(a) and the prevalence of myocardial scar. Regression models were examined in the following manner: unadjusted models were fitted first (model 1); followed by adjusted models for age, sex, race/ethnicity, and body mass index (model 2); and finally, fully adjusted models that included minimal adjustments along with HDL and LDL levels, triglyceride levels, use of lipid-lowering therapy, cigarette smoking status, glomerular filtration rate, systolic and diastolic blood pressure, use of antihypertensive medication, diabetes status, and income. Covariates were chosen a priori on the basis of clinical relevance or their biologic impact on the outcomes deduced from earlier studies. Lp(a) was retained in all models as the exposure variable.

As sensitivity analyses, the fully adjusted model was repeated to examine the potential influence of ischemic heart disease and aortic stenosis as confounders for the Lp(a) interstitial fibrosis relationship. For these purposes, models were first adjusted for total coronary calcium score, and we also excluded participants who had an interim clinical myocardial infarction and those who had myocardial scar defined by CMR LGE. Further models were created to adjust for aortic valve calcification and severe aortic stenosis as potential confounders, given the established link between Lp(a) and aortic stenosis. Severe aortic stenosis was previously defined in MESA by Whelton et al,[18] as follows: 1) echocardiography (eg, peak velocity ≥4.0 m/s, mean gradient ≥40 mm Hg, aortic valve area <1.0 cm^2); 2) aortic valve replacement (surgical or transcatheter) for documented severe aortic stenosis; 3) aortic valve replacement for moderate aortic stenosis when part of coronary artery bypass graft surgery; or 4) clinical documentation of severe aortic stenosis diagnosis. Finally, although no interactions were observed between race or ethnicity and Lp(a) concerning myocardial fibrosis, the impact of Lp(a) on CVD has been identified as race or ethnicity dependent.[6] To investigate these variations further, a stratified subgroup multivariate analysis was performed, examining the relationship of Lp(a) with both interstitial and replacement myocardial fibrosis across different racial or ethnic groups. All analyses were performed using Stata Statistical Software, release 17 (StataCorp), and figures were created with BioRender.com.

RESULTS

In 2,826 participants who had both Lp(a) and complete CMR data from visit 5, a total of 2,040 participants (48% female patients, with a mean age of 69 ± 9 years) had CMR T1 mapping measures. The distributions of Lp(a) relative to native T1 values and ECV% in this subcohort of 2,040 participants are highlighted in Figures 1A and 1B. Participant characteristics for the subcohort included in the Lp(a) and fibrosis study (n = 2,040) are shown in Table 1. The study group consisted of 47% White, 22% Black, 15% Chinese, and 15% Hispanic participants who were stratified on the basis of Lp(a) clinical cutoffs: <30, 30–50, and >50 mg/dL. Significant differences in Lp(a) levels were observed among the different racial or ethnic groups. No significant associations were found between Lp(a) levels and traditional CV risk factors. However, participants with Lp(a) levels >50 mg/dL were more likely to exhibit higher levels of LDL and HDL cholesterol and lower levels of triglyceride, and they were more likely to be receiving lipid-lowering therapy. LV volumes, mass, ejection fraction, and circumferential strain were similar among the 3 groups. Although the mean ECV did not show significant differences among the 3 Lp(a) groups, the mean native T1 values increased significantly because Lp(a) levels rose across severity categories (Table 1). In addition, participants with Lp(a) levels >50 mg/dL exhibited lower LA emptying fraction when compared with participants with Lp(a) levels <30 mg/dL, with a trend toward increased LA minimal volume that did not reach statistical significance ($P = 0.09$).

INTERSTITIAL CARDIAC FIBROSIS.

Significant correlations were observed between Lp(a) levels and both ECV% and native T1 time (Table 2). In a fully adjusted model, a 1-SD increase in log-transformed Lp(a)

corresponded to a 0.2% increase in ECV% and a 4-ms increase in native T1 time. These results remained consistent after excluding participants with an interim myocardial infarction or myocardial scar and after controlling for total coronary calcium score. Moreover, adjusting for aortic valve calcification and excluding participants with severe aortic stenosis did not alter the associations of Lp(a) with markers of interstitial cardiac fibrosis (Table 3).

When Lp(a) levels were stratified into quartiles on the basis of the available ECV and native T1 data, participants in the highest Lp(a) quartile exhibited a significant association with being in the highest ECV% quartile (β: 0.6; 95% CI: 0.1–1.1; $P = 0.01$) when compared with the lowest Lp(a) quartile (Supplemental Table 1). Additionally, there was a significant incremental increase in native T1 time as Lp(a) quartiles increased. Lp(a) was also associated with increased native T1 time when stratified using the clinical cutoff of 50 mg/dL (β = 7; 95% CI: 0.2–13) (Supplemental Table 2). No significant interactions were observed between Lp(a) and measures of interstitial cardiac fibrosis among the different racial or ethnic groups, although White and Hispanic individuals had higher native T1 times (Supplemental Table 3).

Applying severity cutoffs for ECV% and native T1 time that were previously shown to reflect increased risk of adverse outcomes (≥30% and ≥955 ms, respectively), we found that elevated Lp(a) levels were associated with a greater likelihood of worse interstitial cardiac fibrosis (Table 4). In a fully adjusted model, each log unit of Lp(a) was associated with a 20% increased likelihood of having ECV% ≥30% and native T1 times ≥955 ms, respectively. Similar findings were observed after controlling for total coronary and aortic calcium score and excluding participants with interim myocardial infarction and those with myocardial scar by CMR LGE, as well as those patients with severe aortic stenosis.

MYOCARDIAL SCAR.

Contrast-enhanced CMR was conducted on 1,262 participants, and 105 (8%) of these patients had a myocardial scar. Of these participants, 86.9% were men and 13.1% were women. We assessed the associations between Lp(a) levels and the presence of myocardial scar and found a significantly increased likelihood of having a myocardial scar in participants with Lp(a) levels ≥30 mg/dL (OR: 1.85; 95% CI: 1.1–3.2; $P = 0.025$) and ≥50 (OR: 1.9; 95% CI: 1.1–3.4; $P = 0.02$) across all models (Table 5). However, when adjusting for aortic valve calcification and clinically manifested aortic stenosis, the association was less significant when the Lp(a) cutoff of 50 mg/dL was used, compared with a cutoff of 30 mg/dL (Table 6). Nevertheless, those patients with an Lp(a) level ≥30 mg/dL had increased odds of having myocardial scar after adjusting or excluding those patients with any evidence of aortic valve calcification or clinically manifested aortic stenosis. No significant interactions were observed on the basis of on race or ethnicity; however, when stratified by race or ethnicity, White participants demonstrated a slightly greater likelihood of having a myocardial scar (OR: 2.2; 95% CI: 1.03–4.6; $P = 0.04$) when Lp(a) levels were ≥30 mg/dL. Furthermore, no significant difference was observed in the distribution of ischemic and nonischemic scars for both Lp(a) cutoffs of 30 mg/dL (36% vs 36%; $P = 0.9$) and 50 mg/dL (24% vs 23%; $P = 0.9$).

CARDIAC STRUCTURE AND FUNCTION.

Participant characteristics for the entire cohort with complete cine and tagging CMR data at visit 5 (n = 2,826) are detailed in Supplemental Table 4. The entire cohort was included in the study probing associations of Lp(a) with LA and LV cardiac remodeling parameters. Lp(a) was significantly associated with minimal LA indexed volume and LA emptying function, whereas no correlations were found with the parameter of LV structure or function, including LV circumferential strain (Table 7). In a fully adjusted model, a 1-SD increase in log-transformed Lp(a) corresponded to a 0.3 mL/m^2 increase in minimal LA indexed volume, as well as a 0.5% decrease in LA emptying function. These relationships persisted after excluding participants with an interim myocardial infarction or myocardial scar and after controlling for total coronary calcium score (Table 7). Furthermore, adjusting for aortic valve calcification score while excluding individuals with severe aortic stenosis did not alter these associations (Table 8).

DISCUSSION

In this study, we examined the relationship between Lp(a) levels and subclinical interstitial and replacement cardiac fibrosis in a diverse community cohort of 2,040 participants with native T1 time and 1,262 participants who underwent ECV and LGE analysis. Moreover, we studied the relationship between elevated Lp(a) serologic levels and cardiac remodeling, including LV and LA remodeling among 2,826 participants who had complete cine and tagging CMR data at MESA examination 5. We discovered that higher Lp(a) levels correlated with increased markers of subclinical IMF (ECV% and native T1 time), independent of age, sex, race or ethnicity, and traditional CV risk factors (Central Illustration). This association persisted after controlling for total coronary artery calcium score and excluding participants with interim myocardial infarction or myocardial scar defined by CMR LGE, as well as those patients who had clinically manifested aortic stenosis or evidence of aortic valve calcification. Using ECV and native T1 clinical cutoffs that have been associated with worse CV outcomes, we found that increased levels of Lp(a) significantly raised the likelihood of having ECV >30% and native T1 time >955 ms. Participants with Lp(a) levels above 50 mg/dL had higher native T1 times, and patients with levels above 30 mg/dL had greater odds of having myocardial scar on LGE (Central Illustration). Additional analysis on the associations of Lp(a) with parameters of cardiac structure and function demonstrated a positive correlation between Lp(a) and minimum LA volume index, as well as an inverse relationship between Lp(a) and LA emptying function.

INTERSTITIAL MYOCARDIAL FIBROSIS AND LP(a).

In this study, we found that higher levels of Lp(a) were associated with greater diffuse cardiac fibrosis, as well as an increased probability of reaching T1 mapping thresholds associated with greater all-cause mortality and untoward CV outcomes.[2] In a previous MESA longitudinal study by Steffen et al,[19] White participants with elevated Lp(a) levels had an increased risk of incident HFpEF (per log unit Lp[a] [HR: 1.48; $P = 0.001$], Lp[a] ≥30 mg/dL [HR: 2.15; $P = 0.01$)] and Lp[a] ≥50 mg/dL [HR: 2.60; $P = 0.004$]). Additionally, both the Atherosclerosis Risk In Communities study and the Copenhagen City Heart Study documented associations between elevated Lp(a) levels and a greater risk of

heart failure hospitalization. However, in both studies, this link was in part mediated by ischemic heart disease because the relationships were weakened after exclusion of patients who had experienced a myocardial infarction.[20,21] In our study, however, after excluding participants who experienced interim myocardial infarction or had myocardial scars defined by CMR LGE, the association between elevated Lp(a) and fibrosis remained significant, even after controlling for total coronary calcium score. This finding suggests that the link between Lp(a) and interstitial fibrosis is largely independent of coronary artery disease or LV remodeling secondary to myocardial infarction.

Importantly also, we performed analyses controlling for the presence of clinically manifested aortic stenosis (moderate to severe), as well as any evidence of aortic valve calcification, which practically excludes significant aortic stenosis altogether, given that MESA participants at baseline were at least 45 years of age, had no history of previous heart disease, and were therefore highly unlike to have significant aortic valve disease in the absence of valve calcification. These results thus suggest that the association between Lp(a) and IMF reported here is not significantly confounded by myocardial remodeling induced by valvular aortic stenosis and is possibly secondary to a direct effect of Lp(a) on myocardial fibrogenesis.

Indeed, the mechanisms linking Lp(a) to IMF can at least in part be attributed to the oxidative stress pathway combined with inflammation, which is a critical factor in the development of diffuse cardiac fibrosis.[6,22,23] Oxidized phospholipids present on Lp(a) particles can activate various proinflammatory pathways, thereby leading to the recruitment of inflammatory cells to the myocardium.[22,23] In turn, these inflammatory cells may produce reactive oxygen species and cytokines that promote fibroblast activation and ECM synthesis.[6] Another potential mechanism includes the activation of the transforming growth factor (TGF)-β signaling pathway.[24] TGF-β is a key profibrotic cytokine that has been implicated in the pathogenesis of diffuse cardiac fibrosis.[24] Studies have shown that Lp(a) can upregulate TGF-β expression in vascular smooth muscle cells, and TGF-β signaling can lead to the differentiation of fibroblasts into myofibroblasts, thereby promoting ECM synthesis and fibrotic tissue deposition.[25,26] Finally, Lp(a) can directly interact with fibroblasts and modulate their function, thus promoting fibrosis. The combination of the processes mentioned earlier ultimately affects diastolic function, resulting in increased LV filling pressures and the development of heart failure with preserved ejection fraction (HFpEF), potentially through enhancing reactive interstitial cardiac fibrosis. This underscores the significance of understanding the role of elevated Lp(a) levels in promoting interstitial cardiac fibrosis and adverse cardiac remodeling, therefore influencing the pathogenesis of HFpEF.

MYOCARDIAL SCAR AND LP(a).

Further analyses revealed that participants with Lp(a) levels of either >30 mg/dL or >50 mg/dL had an increased risk of having a myocardial scar on CMR LGE. However, a threshold of 30 mg/dL demonstrated a greater propensity for unfavorable CV outcomes than the 50 mg/dL cutoff, thus serving as a more accurate identifier of participants at heightened risk. There was no difference in risk between ischemic and nonischemic scars.

Data on the association between Lp(a) and the presence of myocardial scar defined by CME LGE in the general population are scarce. In an observational study conducted by Vassiliou et al,[27] comprising 110 patients with aortic stenosis of varying degrees of severity, there was no association between Lp(a) and the presence of myocardial scar. Conversely, the current research involved a significantly larger sample size from a prospective study that recruited multiethnic participants without a history of heart disease at baseline. The study revealed that elevated Lp(a) levels were linked to an increased likelihood of detecting myocardial scarring through CMR LGE even after excluding those patients who had clinically significant aortic stenosis or any evidence of aortic valve calcification. The basis for the increased myocardial scar risk may lie in the prothrombotic properties of Lp(a).[28] Studies have shown that high Lp(a) levels have been found to impair the fibrinolytic system, thereby obstructing clot dissolution.[29] This interference may subsequently lead to a heightened accumulation of microthrombi, ultimately increasing the risk of focal and diffuse myocardial fibrosis.[30] However, the direct effect of Lp(a) on myofibroblast activation and matrix collagen deposition may also lead to scar formation combined or not with enhanced interstitial fibrogenesis.

CLINICAL IMPLICATION FOR CARDIOVASCULAR DISEASE DEVELOPMENT, INCLUDING HEART FAILURE.

Although Lp(a) augmentation has been linked to incident heart failure,[19–21] the mechanisms by which such an increase in Lp(a) leads to heart failure remain unknown. Our study provides a potential window of understanding into the pathogenesis of Lp(a)-related incident heart failure (particularly HFpEF), through further elucidating the causation pathway leading from increased Lp(a) to cardiac remodeling and dysfunction in the absence of myocardial infarction and aortic stenosis. Our results suggest that such a pathway includes interstitial fibrogenesis leading to myocardial stiffness and dysfunction with LA enlargement and dysfunction as early alterations in the pathogenesis chain leading to HFpEF. Indeed, in MESA, an Lp(a) increase has been linked primarily to HFpEF, before and after the exclusion of participants with interim myocardial infarction and clinically manifested coronary artery disease.[19] Abnormal atrioventricular coupling has been implicated in the genesis not only of heart failure, but also of atrial fibrillation and CV events in clinical and population studies.[31,32] Our findings demonstrate a link between Lp(a) increase and LA enlargement and dysfunction that has direct clinical implications for incident atrial fibrillation and stroke in association with elevated serum levels of Lp(a). Additionally, through enhancing the risk of myocardial scar formation, high Lp(a) may also lead to ventricular arrhythmias, which may further contribute to poorer CV outcomes.[28]

Lp(a) augmentation may cause or contribute to myocardial ECM remodeling through up-regulation of profibrotic factors such as TGF-β_1 and the stimulation of inflammatory pathways. Our findings support the concept that such alterations eventually lead to myocardial tissue stiffening and architectural disorganization with secondary atrial enlargement and dysfunction. Further mechanistic studies are warranted to elucidate fully both atrial and ventricular myopathy in association with Lp(a) increase. If confirmed in further clinical studies, the study results could influence early detection, monitoring, and risk stratification through routine Lp(a) testing of individuals at risk for heart failure,

atrial fibrillation, and stroke. Lp(a) testing may also influence the management of patients with heart failure, particularly HFpEF, as well as those with atrial fibrillation, and may possibly help to guide treatment decisions.[33] Hopefully, understanding the role of Lp(a) in myocardial fibrogenesis can inform the development of novel therapies aimed at reducing Lp(a) levels to modulate IMF, thus reducing the burden of heart failure and CV diseases in the future.

STUDY LIMITATIONS.

This study features a diverse group of patients with available T1 mapping and Lp(a) measurements. The MESA cohort comprises participants of different ethnicities and backgrounds, a feature that enables the exploration of associations across a range of demographic groups through standardized protocols. However, the analysis is cross-sectional and thus can establish only associations and not causation. Longitudinal studies are required to determine temporal relationships between Lp(a) levels and myocardial fibrogenesis. Furthermore, we cannot rule out residual confounding, as well as selection bias, because participants in MESA may not be entirely representative of the general population, thereby potentially limiting the generalizability of the study findings. Finally, whereas native T1 and ECV maps are used in the evaluation of myocardial fibrosis, their lack of specificity for individual diseases requires that findings be examined within the scope of particular clinical settings.[34] Although the primary cause of ECM expansion is fibrosis, other factors such as edema, hypertrophy, or additional infiltrative cardiac conditions may also play a role.[35] Conversely, CMR T1 mapping techniques are known to offer a reliable and noninvasive means of assessing myocardial fibrosis, particularly in long-term settings, as in the case of this study.[1] Native T1 does not necessitate the administration of contrast agents, thus making it a suitable option for the follow-up of patients with specific comorbidities such as kidney impairment.[34]

CONCLUSIONS

This population-based cohort study offers evidence demonstrating a significant association between elevated Lp(a) levels and both interstitial and replacement myocardial fibrosis. Our results also demonstrate an association between Lp(a) increase and LA remodeling, thereby emphasizing the necessity for additional prospective studies to investigate the crucial role of Lp(a)e as a potential contributor to the onset and progression of cardiac fibrosis across disease processes leading to atrial fibrillation and heart failure. Further understanding the interconnections among Lp(a), myocardial fibrosis, and cardiac remodeling could potentially lead to the development of novel targeted prevention and treatment strategies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

The authors thank the other investigators, the staff, and the participants of the MESA study for their valuable contributions. A full list of participating MESA investigators and institutions can be found on the MESA website. The views expressed in this paper are those of the authors and do not necessarily represent the views of the National

Heart, Lung, and Blood Institute; the National Institutes of Health; or the U.S. Department of Health and Human Services. The data underlying this paper were obtained as part of the National Institutes of Health–sponsored MESA (Multi-Ethnic Study of Atherosclerosis) by permission. Data will be shared on request to the corresponding author with permission of the MESA steering committee.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

This work was supported by contracts HHSN268201500003I, N01-HC-95159, N01-HC95160, N01-HC-95161, N01-HC-95162, N01-HC-95163, N01-HC-95164, N01-HC-95165, N01HC-95166, N01-HC-95167, N01-HC-95168, and N01-HC-95169 and by grant R01-HL-127659 from the National Heart, Lung, and Blood Institute; by grants UL1- TR-000040, UL1-TR001079, and UL1-TR-001420 from the National Center for Advancing Translational Sciences; and by a grant from Bayer Healthcare for the use of gadolinium contrast agent. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ABBREVIATIONS AND ACRONYMS

CMR	cardiac magnetic resonance
CV	cardiovascular
CVD	cardiovascular disease
ECM	extracellular matrix
ECV	extracellular volume
ECV%	extracellular volume fraction
HDL	high-density lipoprotein
HFpEF	heart failure with preserved ejection fraction
IMF	interstitial myocardial fibrosis
LA	left atrial
LDL	low-density lipoprotein
LGE	late gadolinium enhancement
Lp(a)	lipoprotein(a)
LV	left ventricular
TGF	transforming growth factor

REFERENCES

1. Ambale-Venkatesh B, Lima JA. Cardiac MRI: a central prognostic tool in myocardial fibrosis. Nat Rev Cardiol 2015;12:18–29. 10.1038/nrcardio.2014.159 [PubMed: 25348690]
2. Marques MD, Weinberg R, Kapoor S, et al. Myocardial fibrosis by T1 mapping magnetic resonance imaging predicts incident cardiovascular events and all-cause mortality: the Multi-Ethnic Study of Atherosclerosis. Eur Heart J Cardiovasc Imaging. 2022;23:1407–1416. 10.1093/ehjci/jeac010 [PubMed: 35147665]
3. Raisi-Estabragh Z, McCracken C, Hann E, et al. Incident clinical and mortality associations of myocardial native T1 in the UK Biobank. J Am Coll Cardiol Img 2023;16(4):450–460. 10.1016/j.jcmg.2022.06.011

4. Turkbey EB, Nacif MS, Guo M, et al. Prevalence and correlates of myocardial scar in a US cohort. JAMA. 2015;314:1945–1954. 10.1001/jama.2015.14849 [PubMed: 26547466]
5. Webber M, Jackson SP, Moon JC, Captur G. myocardial fibrosis in heart failure: anti-fibrotic therapies and the role of cardiovascular magnetic resonance in drug trials. Cardiol Ther 2020;9:363–376. 10.1007/s40119-020-00199-y [PubMed: 32862327]
6. Tsimikas S A Test in Context: Lipoprotein(a): diagnosis, prognosis, controversies, and emerging therapies. J Am Coll Cardiol 2017;69:692–711. 10.1016/j.jacc.2016.11.042 [PubMed: 28183512]
7. Mehta A, Vasquez N, Ayers CR, et al. Independent association of lipoprotein(a) and coronary artery calcification with atherosclerotic cardiovascular risk. J Am Coll Cardiol 2022;79:757–768. 10.1016/j.jacc.2021.11.058 [PubMed: 35210030]
8. Marques MD, Nauffal V, Ambale-Venkatesh B, et al. Association between inflammatory markers and myocardial fibrosis. Hypertension. 2018;72: 902–908. 10.1161/HYPERTENSIONAHA.118.11463 [PubMed: 30354713]
9. Tsimikas S, Karwatowska-Prokopczuk E, Gouni-Berthold I, et al. Lipoprotein(a) reduction in persons with cardiovascular disease. N Engl J Med 2020;382:244–255. 10.1056/NEJMoa1905239 [PubMed: 31893580]
10. Bild DE, Bluemke DA, Burke GL, et al. Multi-Ethnic Study of Atherosclerosis: objectives and design. Am J Epidemiol 2002;156:871–881. 10.1093/aje/kwf113 [PubMed: 12397006]
11. Multi-Ethnic Study of Atherosclerosis (MESA). Website. Accessed February 7, 2023. https://www.mesa-nhlbi.org
12. Mackey RH, Greenland P, Goff DC, et al. High-density lipoprotein cholesterol and particle concentrations, carotid atherosclerosis, and coronary events: MESA (multi-ethnic study of atherosclerosis). J Am Coll Cardiol 2012;60:508–516. 10.1016/j.jacc.2012.03.060 [PubMed: 22796256]
13. Tsai MY, Johnson C, Kao WH, et al. Cholesteryl ester transfer protein genetic polymorphisms, HDL cholesterol, and subclinical cardiovascular disease in the Multi-Ethnic Study of Atherosclerosis. Atherosclerosis. 2008;200: 359–367. 10.1016/j.atherosclerosis.2007.12.038 [PubMed: 18243217]
14. Marcovina SM, Albers JJ, Scanu AM, et al. Use of a reference material proposed by the International Federation of Clinical Chemistry and Laboratory Medicine to evaluate analytical methods for the determination of plasma lipoprotein(a). Clin Chem 2000;46:1956–1967. [PubMed: 11106328]
15. Liu CY, Liu YC, Wu C, et al. Evaluation of age-related interstitial myocardial fibrosis with cardiac magnetic resonance contrast-enhanced T1 mapping: MESA (Multi-Ethnic Study of Atherosclerosis). J Am Coll Cardiol 2013;62:1280–1287. 10.1016/j.jacc.2013.05.078 [PubMed: 23871886]
16. Donekal S, Venkatesh BA, Liu YC, et al. Interstitial fibrosis, left ventricular remodeling, and myocardial mechanical behavior in a population-based multiethnic cohort: the Multi-Ethnic Study of Atherosclerosis (MESA) study. Circ Cardiovasc Imaging. 2014;7:292–302. 10.1161/CIRCIMAGING.113.001073 [PubMed: 24550436]
17. Habibi M, Chahal H, Opdahl A, et al. Association of CMR-measured LA function with heart failure development: results from the MESA study. J Am Coll Cardiol Img 2014;7:570–579. 10.1016/j.jcmg.2014.01.016
18. Whelton SP, Jha K, Dardari Z, et al. Prevalence of aortic valve calcium and the long-term risk of incident severe aortic stenosis. J Am Coll Cardiol Img Published online March 30, 2023. 10.1016/j.jcmg.2023.02.018
19. Steffen BT, Duprez D, Bertoni AG, et al. Lp(a) [lipoprotein(a)]-related risk of heart failure is evident in Whites but not in other racial/ethnic groups. Arterioscler Thromb Vasc Biol 2018;38: 2498–2504. 10.1161/ATVBAHA.118.311220 [PubMed: 30354212]
20. Kamstrup PR, Nordestgaard BG. Elevated lipoprotein(a) levels, LPA risk genotypes, and increased risk of heart failure in the general population. J Am Coll Cardiol HF. 2016;4:78–87. 10.1016/j.jchf.2015.08.006

21. Agarwala A, Pokharel Y, Saeed A, et al. The association of lipoprotein(a) with incident heart failure hospitalization: Atherosclerosis Risk in Communities study. Atherosclerosis. 2017;262:131–137. 10.1016/j.atherosclerosis.2017.05.014 [PubMed: 28554015]
22. Steinberg D, Witztum JL. Oxidized low-density lipoprotein and atherosclerosis. Arterioscler Thromb Vasc Biol 2010;30:2311–2316. 10.1161/ATVBAHA.108.179697 [PubMed: 21084697]
23. Spence JD, Koschinsky M. Mechanisms of lipoprotein(a) pathogenicity: prothrombotic, proatherosclerotic, or both? Arterioscler Thromb Vasc Biol 2012;32:1550–1551. 10.1161/ATVBAHA.112.251306 [PubMed: 22699275]
24. Caplice NM, Panetta C, Peterson TE, et al. Lipoprotein (a) binds and inactivates tissue factor pathway inhibitor: a novel link between lipoproteins and thrombosis. Blood. 2001;98:2980–2987. 10.1182/blood.v98.10.2980 [PubMed: 11698280]
25. Walton KL, Johnson KE, Harrison CA. Targeting TGF-beta mediated SMAD signaling for the prevention of fibrosis. Front Pharmacol 2017;8: 461. 10.3389/fphar.2017.00461 [PubMed: 28769795]
26. Kojima S, Harpel PC, Rifkin DB. Lipoprotein (a) inhibits the generation of transforming growth factor beta: an endogenous inhibitor of smooth muscle cell migration. J Cell Biol 1991;113:1439–1445. 10.1083/jcb.113.6.1439 [PubMed: 1828468]
27. Vassiliou VS, Flynn PD, Raphael CE, et al. Lipoprotein(a) in patients with aortic stenosis: insights from cardiovascular magnetic resonance. PLoS One. 2017;12:e0181077. 10.1371/journal.pone.0181077 [PubMed: 28704465]
28. Marcovina SM, Koschinsky ML. Evaluation of lipoprotein(a) as a prothrombotic factor: progress from bench to bedside. Curr Opin Lipidol 2003;14: 361–366. 10.1097/00041433-200308000-00004 [PubMed: 12865733]
29. Angles-Cano E, de la Pena Diaz A, Loyau S. Inhibition of fibrinolysis by lipoprotein(a). Ann N Y Acad Sci 2001;936:261–275. 10.1111/j.1749-6632.2001.tb03514.x [PubMed: 11460483]
30. Angles-Cano E, Hervio L, Rouy D, et al. Effects of lipoprotein(a) on the binding of plasminogen to fibrin and its activation by fibrin-bound tissue-type plasminogen activator. Chem Phys Lipids. 1994;67–68:369–380. 10.1016/0009-3084(94)90159-7
31. Pezel T, Venkatesh BA, De Vasconcellos HD, et al. Left atrioventricular coupling index as a prognostic marker of cardiovascular events: the MESA study. Hypertension. 2021;78:661–671. 10.1161/HYPERTENSIONAHA.121.17339 [PubMed: 34225471]
32. Pezel T, Ambale-Venkatesh B, Quinaglia T, et al. Change in left atrioventricular coupling index to predict incident atrial fibrillation: the Multi-Ethnic Study of Atherosclerosis (MESA). Radiology. 2022;303:317–326. 10.1148/radiol.210315 [PubMed: 35191736]
33. Willeit P, Kiechl S, Kronenberg F, et al. Discrimination and net reclassification of cardiovascular risk with lipoprotein(a): prospective 15-year outcomes in the Bruneck study. J Am Coll Cardiol 2014;64:851–860. 10.1016/j.jacc.2014.03.061 [PubMed: 25169167]
34. Robinson AA, Chow K, Salerno M. Myocardial T1 and ECV measurement: underlying concepts and technical considerations. J Am Coll Cardiol Img 2019;12:2332–2344. 10.1016/j.jcmg.2019.06.031
35. Wong TC, Piehler K, Meier CG, et al. Association between extracellular matrix expansion quantified by cardiovascular magnetic resonance and short-term mortality. Circulation. 2012;126:1206–1216. 10.1161/CIRCULATIONAHA.111.089409 [PubMed: 22851543]

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE:

Elevated blood levels of Lp(a) are associated with both IMF and replacement fibrosis (myocardial scar), independent of age, race, conventional CV risk factors, and interim cardiovascular events, thus supporting a causal link between Lp(a) and subclinical CVD.

TRANSLATIONAL OUTLOOK:

These findings may form the basis for the development of therapeutic strategies targeting Lp(a) to mitigate cardiac fibrosis and scarring. Further research is needed to uncover the mechanisms by which Lp(a) adversely affects CV health.

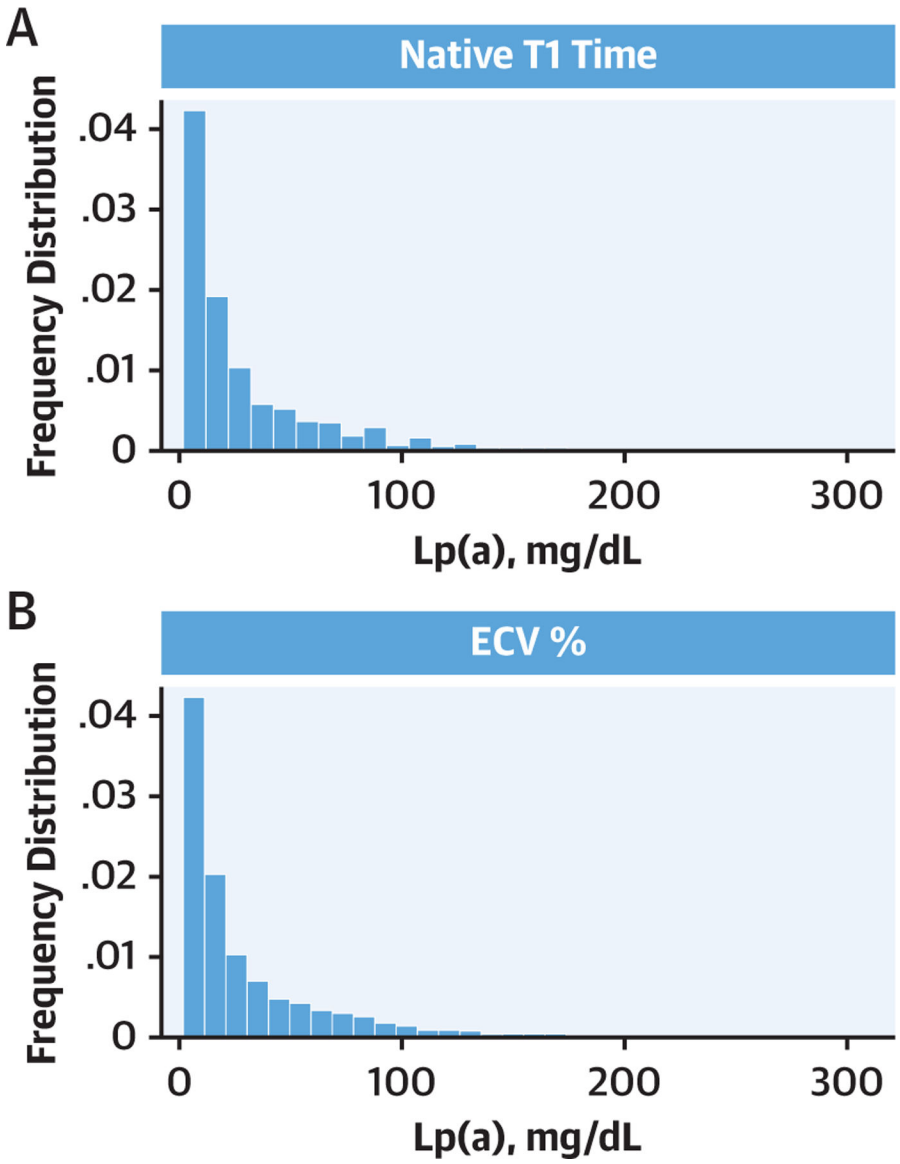
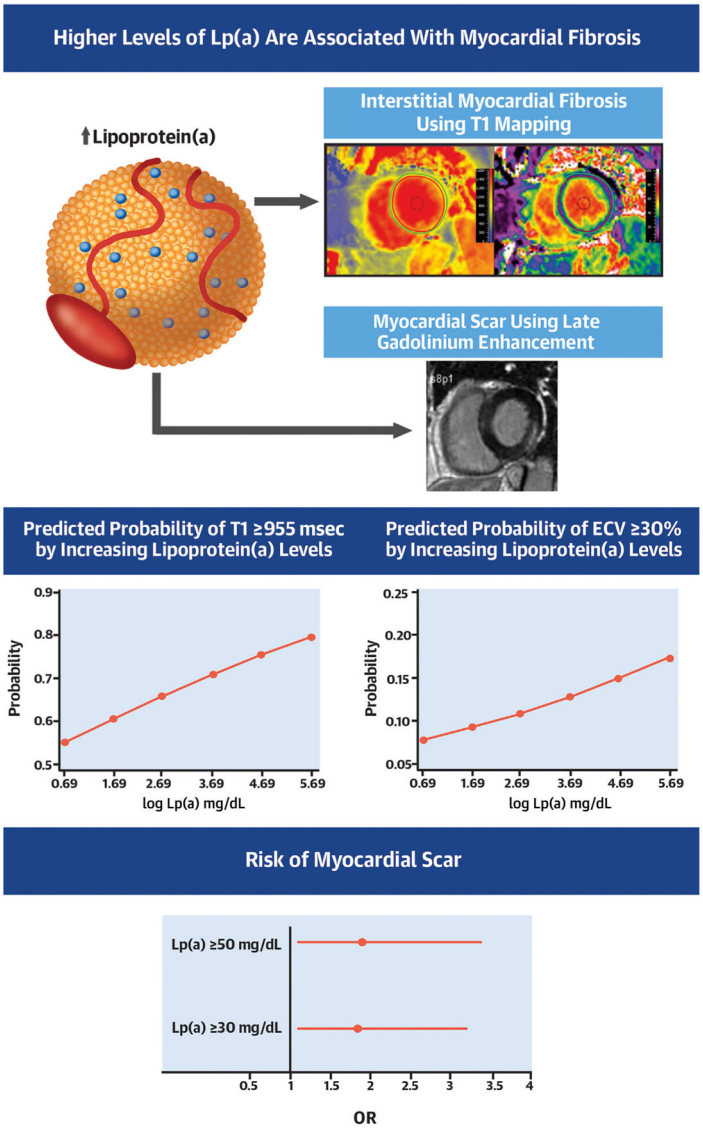


FIGURE 1.

Lp(a) Distribution Histogram Among Participants With Cardiac Magnetic Resonance T1 Mapping in MESA

Positively skewed distribution of lipoprotein(a) (Lp[a]) among those patients with available (A) native T1 time and (B) percentage of extracellular volume (ECV%).



Chehab O, et al. J Am Coll Cardiol. 2023;82(24):2280–2291.

CENTRAL ILLUSTRATION.

Lipoprotein(a) Is Associated With Interstitial Cardiac Fibrosis and Myocardial Scar

(Top) Lipoprotein(a) (Lp[a]) was found to be associated with both interstitial and replacement myocardial fibrosis independent of aortic valve calcification and major adverse cardiovascular events. (Middle) Multivariate regression analysis highlighting the increased probability of reaching clinical interstitial fibrosis cutoff thresholds of native T1 time of 955 ms and percentage of extracellular volume (ECV%) of 30% with each SD unit increase in lipoprotein(a). (Bottom) Forest plot demonstration of both lipoprotein(a) of at least 30 and 50 mg/dL linked to greater risk of myocardial scar in a fully adjusted model.

J Am Coll Cardiol. Author manuscript; available in PMC 2025 January 14.

TABLE 1

Clinical Characteristics of Participants Who Underwent Cardiac Magnetic Resonance T1 Mapping Stratified by Lp(a) Categories

	Lp(a) Categories			
	<30 mg/dL (n = 1,426; 70%)	**30 and <50 mg/dL (n = 236; 12%)**	**≥50 mg/dL (n = 378; 18%)**	***P* Value**
Age, y	67 (61–75)	69 (61–75)	70 (61–76)	0.30
Female	717 (50)	109 (46)	147 (39)	<0.001
Body mass index, kg/m^2	27 (24–31)	27 (24–31)	27 (24–31)	0.70
Race/ethnicity				<0.001
White	718 (50)	99 (42)	151 (40)	
Black	207 (14)	83 (35)	162 (43)	
Chinese	250 (18)	29 (12)	35 (9)	
Hispanic	251 (18)	25 (11)	30 (8)	
Current smoking				0.30
Never	662 (46)	101 (43)	180 (48)	
Former	666 (47)	115 (49)	163 (43)	
Current	98 (7)	20 (8)	35 (9)	
Diabetes mellitus status				0.20
None	885 (62)	161 (68)	257 (68)	
Prediabetes	302 (21)	43 (18)	59 (16)	
Type 2 diabetes	239 (17)	32 (14)	62 (16)	
Heart rate, beats/min	63 (57–70)	65 (57–71)	62 (56–69)	0.10
Systolic blood pressure, mm Hg	118 (108–133)	118 (109–132)	120 (108–136)	0.40
Diastolic blood pressure, mm Hg	68 (61–75)	68 (62–75)	68 (61–74)	0.40
Hypertension medication	724 (51)	118 (50)	208 (55)	0.30
LDL cholesterol, mg/dL	102 (81–126)	106 (87–128)	111 (90–134)	<0.001
HDL cholesterol, mg/dL	52 (43–62)	53 (45–66)	56 (47–68)	<0.001
Triglycerides, mg/dL	101 (72–138)	88 (66–129)	89 (68–120)	<0.001
Lipid-lowering medication	520 (36)	73 (31)	176 (47)	<0.001
eGFR, mL/min/1.73 m^2	80 (68–93)	83 (68–94)	81 (68–92)	0.60
Aortic valve calcification at baseline examination	278 (19.5)	37 (16)	83 (22)	0.20
Severe aortic stenosis	13 (0.9)	3 (1.3)	5 (1.3)	0.70

	Lp(a) Categories			
	<30 mg/dL (n = 1,426; 70%)	**30 and <50 mg/dL (n = 236; 12%)**	**≥50 mg/dL (n = 378; 18%)**	***P* Value**
LV end-diastolic volume indexed to body surface area, mL/m^2	63.6 (55.7–71.7)	64.7 (56.2–72.6)	61.9 (54.4–71.4)	0.30
LV end-systolic volume indexed to body surface area, mL/m^2	23.1 (19.0–28.5)	23.7 (18.9–29.2)	23.0 (18.5–28.9)	0.60
LV end-diastolic mass indexed to body surface area, g/m^2	63.4 (55.6–72.2)	62.7 (55.3–72.9)	62.7 (55.6–72.4)	0.90
LV ejection fraction, %	62.9 (58.0–67.3)	62.8 (57.9–66.9)	62.4 (57.9–66.9)	0.60
LV circumferential strain, %	−17 (−19 to −14)	−17 (−19 to −14)	−16 (−18 to −14)	0.20
ECV, %[a]	26.58 (24.86–28.38)	26. (25–28)	27 (25–29)	0.10
Native T1 time, ms	968 (941–998)	974 (947–1,000)	978 (952–1,004)	<0.001
Myocardial scar[a]	67 (8)	13 (9)	25 (11)	0.20
Maximal LA volume indexed to body surface area, mL/m^2	32.8 (26.4–40.9)	32.7 (27.2–39.6)	34.6 (27.6–40.9)	0.50
Minimal LA volume indexed to body surface area, mL/m^2	14.2 (10.2–19.1)	14.3 (10.8–18.3)	14.9 (10.5–20.5)	0.09
LA emptying fraction, %	56.8 (49.9–63.8)	56.0 (50.1–62.7)	54.4 (48.2–62.7)	0.04
LA strain, %	32 (25–38)	31 (25–40)	31 (25–40)	0.90

Values are median (Q1-Q3) or n (%).

[a]ECV and LGE data were available for 1,262 participants: 887 (70%) with Lp(a) <30 mg/dL, 151 (12%) with Lp(a) 30–49 mg/dL, and 224 (18%) with Lp(a) ≥50 mg/dL.

ECV = extracellular volume; eGFR = estimated glomerular filtration rate; HDL = high-density lipoprotein; LA = left atrial; LDL = low-density lipoprotein; Lp(a) = lipoprotein(a); LV = left ventricular.

TABLE 2

Association of Lp(a) as a Continuous Variable With Cardiac Magnetic Resonance-Measures of Interstitial Myocardial Fibrosis

Regression Models	Lp(a) (Log-Transformed)			
	ECV (%) (n = 1,262)		Native T1 (ms) (n = 2,040)	
	β (95% CI)	*P* Value	β (95% CI)	*P* Value
Model 1[a]	0.2 (0.1–0.3)	0.004	5 (3–6)	<0.001
Model 2[b]	0.2 (0.05–0.3)	0.007	4 (3–6)	<0.001
Model 3[c]	0.2 (0.05–0.3)	0.007	4 (2–6)	<0.001
Model 4[d]	0.2 (0.1–0.3)	0.006	4 (2–6)	0.001

[a]Model 1: Unadjusted.

[b]Model 2: Adjusted for age, sex, race/ethnicity, body mass index.

[c]Model 3: Adjusted for variables included in model 2, high- and low-density lipoprotein levels, use of lipid-lowering therapy, triglyceride levels, cigarette smoking status, glomerular filtrate rate, systolic and diastolic blood pressure, use of antihypertensive medication, diabetes status, and income.

[d]Model 4: Adjusted for variables included in model 3, in addition to total coronary calcium score and excluding those patients with myocardial scar and interim myocardial infarction.

Abbreviations as in Table 1.

TABLE 3

Association Between Lp(a) Levels and Cardiac Magnetic Resonance-Measures of Interstitial Myocardial Fibrosis After Controlling for Aortic Valve Calcification and Moderate to Severe Aortic Stenosis

	ECV (%)		Native T1 (ms)	
Lp(a) mg/dL (Log)	**β (95% CI)**	***P* Value**	**β (95% CI)**	***P* Value**
Model 1[a]	0.2 (0.04–0.3)	0.01	4 (2–6)	<0.001
Model 2[b]	0.2 (0.05–0.3)	0.007	4 (3–6)	<0.001
Model 3[c]	0.2 (0.05–0.3)	0.005	4 (2–6)	<0.001
Model 4[d]	0.2 (0.06–0.3)	0.004	4 (2–5.5)	<0.001

[a]Model 1: Adjusted for age, sex, race/ethnicity, body mass index, high- and low-density lipoprotein levels, use of lipid-lowering therapy, triglyceride levels, cigarette smoking status, glomerular filtrate rate, systolic and diastolic blood pressure, use of antihypertensive medication, diabetes status, income, and whether there was evidence of aortic valve calcium from baseline visit.

[b]Model 2: Adjusted for the same variables as model 1 but excluding those patients who had evidence of any aortic valve calcification from the baseline examination (ECV, n = 1,162; native T1 time, n = 1,858).

[c]Model 3: Adjusted for the same variables as model 1 and those patients who had evidence of clinically severe aortic stenosis.

[d]Model 4: Adjusted for the same variables as model 1 but excluding those patients who had evidence of clinically manifested moderate to severe aortic stenosis (ECV, n = 1,251; native T1 time, n = 2,019).

Abbreviations as in Table 1.

TABLE 4

Association Between Lp(a) Levels and Increased Risk of Exceeding Clinical Thresholds for Interstitial Myocardial Fibrosis in MESA

Regression Models	Lp(a) (Log-Transformed)			
	ECV ≥30%		Native T1 ≥955 ms	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Model 1[a]	1.2 (1.02–1.40)	0.03	1.3 (1.2–1.4)	<0.001
Model 2[b]	1.2 (1.01–1.34)	0.03	1.3 (1.2–1.4)	<0.001
Model 3[c]	1.2 (1.04–1.43)	0.01	1.2 (1.1–1.4)	<0.001
Model 4[d]	1.4 (1.1–1.7)	0.002	1.2 (1.1–1.4)	0.006

[a]Model 1: Unadjusted.

[b]Model 2: Adjusted for age, sex, race/ethnicity, and body mass index.

[c]Model 3: Adjusted for variables included in model 2, high- and low-density lipoprotein levels, use of lipid-lowering therapy, triglyceride levels, cigarette smoking status, glomerular filtrate rate, systolic and diastolic blood pressure, use of antihypertensive medication, diabetes status, and income.

[d]Model 4: Adjusted for variables included in model 3 and total coronary calcium score and excluding patients those with myocardial scar, interim myocardial infarction, and severe aortic stenosis.

Abbreviations as in Table 1.

TABLE 5

Lp(a) Relationship With Myocardial Scar Among 1,262 MESA Participants

	Myocardial Scar					
	Lp(a) (Log)		Lp(a) ≥30 mg/dL		Lp(a) ≥50 mg/dL	
Models	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Model 1[a]	1.1 (0.9–1.4)	0.20	1.7 (1.1–2.6)	0.02	1.7 (1.1–2.7)	0.02
Model 2[b]	1.2 (0.96–1.4)	0.10	1.7 (1.1–2.7)	0.02	1.8 (1.1–2.8)	0.01
Model 3[c]	1.15 (0.9–1.4)	0.20	1.85 (1.1–3.2)	0.025	1.9 (1.1–3.4)	0.02

[a]Model 1: Adjusted for age, sex, race/ethnicity, body mass index, and race.

[b]Model 2: Adjusted for variables included in model 1, high- and low-density lipoprotein levels, use of lipid-lowering therapy, triglyceride levels, cigarette smoking status, glomerular filtrate rate, systolic and diastolic blood pressure, use of antihypertensive medication, diabetes status, and income.

[c]Model 3: Adjusted for variables included in model 2 and total coronary calcium score.

Lp(a) = lipoprotein(a).

TABLE 6

Lp(a) Relationship With Myocardial Scar After Controlling for Aortic Valve Calcification and Severe Aortic Stenosis

	Myocardial Scar					
	Lp(a) (Log)		Lp(a) ≥30 mg/dL		Lp(a) ≥50 mg/dL	
Models	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Model 1[a]	1.15 (0.9–1.4)	0.10	1.7 (1.1–2.7)	0.02	1.7 (1.0–2.9)	0.05
Model 2[b]	1.2 (0.9–1.4)	0.10	1.8 (1.1–3.0)	0.02	1.7 (0.95–3.1)	0.07
Model 3[c]	1.15 (0.9–1.4)	0.10	1.7 (1.1–2.7)	0.02	1.7 (1.03–2.9)	0.04
Model 4[d]	1.15 (0.9–1.4)	0.10	1.7 (1.1–2.8)	0.01	1.8 (1.05–3)	0.03

[a]Model 1: Adjusted for age, sex, race/ethnicity, body mass index, high- and low-density lipoprotein levels, use of lipid-lowering therapy, triglyceride levels, cigarette smoking status, glomerular filtrate rate, systolic and diastolic blood pressure, use of antihypertensive medication, diabetes status, income, and evidence of aortic valve calcification.

[b]Model 2: Adjusted for the same variables as model 1 and excluding those patients who had evidence of any aortic valve calcification on baseline examination (n = 1,162).

[c]Model 3: Adjusted for the same variables as model 1 and including those patients who had evidence of clinically severe aortic stenosis.

[d]Model 4: Adjusted for the same variables as model 1 but excluding those patients who had evidence of clinically severe aortic stenosis (n = 1,251).

Lp(a) = lipoprotein(a).

TABLE 7

Lp(a) Correlation With Cardiac Structure/Function Among Those Patients Who Underwent Cardiac Magnetic Resonance Cine/Tagging

	Lp(a) (Log-Transformed)					
	Minimal LA Volume Indexed to Body Surface Area, mL/m^2		LA Emptying Fraction, %		LV Circumferential Strain, %	
Models	**β (95% CI)**	***P* Value**	**β (95% CI)**	***P* Value**	**β (95% CI)**	***P* Value**
Model 1[a]	0.3 (0.1–0.7)	0.01	−0.5 (−0.9 to −0.1)	0.006	0.0 (−0.1 to 0.1)	0.40
Model 2[b]	0.3 (0.1–0.6)	0.01	−0.6 (−0.9 to −0.2)	0.001	0.0 (−0.1 to 0.1)	0.60
Model 3[c]	0.3 (0.1–0.6)	0.01	−0.5 (−0.8 to −0.1)	0.01	0.0 (−0.2 to 0.1)	0.30
Model 4[d]	0.4 (0.1–0.7)	0.02	−0.5 (−0.9 to −0.1)	0.02	−0.1 (−0.2 to 0.0)	0.10

[a]Model 1: Unadjusted.

[b]Model 2: Adjusted for age, sex, race/ethnicity, and body mass index.

[c]Model 3: Adjusted for variables included in model 2, high- and low-density lipoprotein levels, use of lipid-lowering therapy, triglyceride levels, cigarette smoking status, glomerular filtrate rate, systolic and diastolic blood pressure, use of antihypertensive medication, diabetes status, and income.

[d]Model 4: Adjusted for variables included in model 3, in addition to total coronary calcium score and excluding those patients with myocardial scar and interim myocardial infarction.

LA = left atrial; Lp(a) = lipoprotein(a); LV = left ventricular.

TABLE 8

Lp(a) Correlation With Cardiac Structure/Function After Controlling for Aortic Valve Calcification and Severe Aortic Stenosis

	Lp(a) (Log-Transformed)					
	Minimal LA Volume Indexed to Body Surface Area, mL/m^2		LA Emptying Fraction, %		LV Circumferential Strain, %	
Models	**β (95% CI)**	***P* Value**	**β (95% CI)**	***P* Value**	**β (95% CI)**	***P* Value**
Model 1[a]	0.3 (0.0–0.5)	0.05	−0.4 (−0.8 to −0.0)	0.02	−0.1 (−0.2 to 0.0)	0.20
Model 2[b]	0.3 (0.0–0.6)	0.05	−0.5 (−0.9 to −0.1)	0.01	0.0 (−0.1 to 0.1)	0.60
Model 3[c]	0.3 (0.0–0.6)	0.05	−0.5 (−0.8 to −0.1)	0.01	−0.1 (−0.2 to 0.0)	0.20
Model 4[d]	0.3 (0.0–0.6)	0.05	−0.5 (−0.8 to −0.1)	0.01	−0.1 (−0.2 to 0.1)	0.30

[a]Model 1: Adjusted for age, sex, race/ethnicity, body mass index, high- and low-density lipoprotein levels, use of lipid-lowering therapy, triglyceride levels, cigarette smoking status, glomerular filtrate rate, systolic and diastolic blood pressure, use of antihypertensive medication, diabetes status, income, and whether there was evidence of aortic valve calcium from baseline visit.

[b]Model 2: Adjusted for the same variables as model 1 but excluding those patients who had evidence of any aortic valve calcification from the baseline examination.

[c]Model 3: Adjusted for the same variables as model 1 and those patients who had evidence of clinically severe aortic stenosis.

[d]Model 4: Adjusted for the same variables as model 1 but excluding those patients who had evidence of clinically manifested moderate to severe aortic stenosis.

Abbreviations as in Table 7.