## Title
Lipoprotein(a) and Risk of Myocardial Infarction and Death in Chronic Kidney Disease



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## Authors
Bajaj, Archna
Damrauer, Scott M
Anderson, Amanda H
et al.

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**Lipoprotein(a) and Risk of Myocardial Infarction and Death in Persons with Chronic Kidney Disease: Findings from the Chronic Renal Insufficiency Cohort (CRIC) Study**

Archna Bajaj, MD; Scott M Damrauer, MD; Amanda H Anderson, PhD, MPH; Dawei Xie, PhD; Matthew J Budoff, MD; Alan S Go, MD; Jiang He, MD, PhD; James P Lash, MD; Akinlolu Ojo, MD, PhD; Wendy S Post, MD, MS; Mahboob Rahman, MD; Muredach P Reilly, MBBCh, MSCE; Danish Saleheen, MBBS, PhD; Raymond R Townsend, MD; Jinbo Chen, PhD; Daniel J Rader, MD and the CRIC Study Investigators*

AUTHOR AFFILIATIONS: Division of General Internal Medicine, Department of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania (AB); Division of Vascular Surgery, University of Pennsylvania, Philadelphia, Pennsylvania (SMD); Corporal Michael J. Crescenz Veterans Affairs Medical Center, Philadelphia, Pennsylvania (SMD); Department of Biostatistics and Epidemiology, Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania, Philadelphia, Pennsylvania (AHA, DX, DS, JC); Department of Medicine, Los Angeles Biomedical Research Institute at Harbor, University of California-Los Angles, Los Angeles, California (MJB); Division of Research, Kaiser Permanente Northern California, Oakland, California (ASG); Department of Epidemiology, Tulane University School of Public Health and Tropical Medicine, New Orleans, Louisiana (JH); Division of Nephrology, Department of Medicine, University of Illinois at Chicago, Chicago, Illinois (JPL); Department of Medicine, University of Michigan, Ann Arbor, Michigan (AO); Department of Epidemiology, Johns Hopkins University Bloomberg School of Public Health, Baltimore, Maryland (WSP); Division of Cardiology, Department of Medicine, Johns Hopkins School of Medicine, Baltimore, Maryland (WSP); Division of Nephrology and Hypertension, Case Western Reserve University, University Hospitals Case Medical Center, Cleveland, Ohio (MR); Division of Cardiology, Department of Medicine, Columbia University, New York, New York (MPR); Irving Institute for Clinical and Translational Research, Columbia University (MPR); Department of Genetics, University of Pennsylvania, Philadelphia,

Pennsylvania (DS, DJR); Division of Kidney, Urologic, and Hematologic Diseases, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland (RRT); Department of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania (DJR); Department of Pediatrics, University of Pennsylvania, Philadelphia, Pennsylvania (DJR); The Penn Cardiovascular Institute, University of Pennsylvania, Philadelphia, Pennsylvania (DJR); Institute for Translational Medicine and Therapeutics, University of Pennsylvania, Philadelphia, Pennsylvania (DJR)

CORRESPONDING AUTHOR: Archna Bajaj, MD, Division of General Internal Medicine, Department of Medicine, University of Pennsylvania, Philadelphia, PA 19104, USA (bajaja@mail.med.upenn.edu)

ABBREVIATED TITLE: Lp(a) and risk of MI and death in CKD

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* The Chronic Renal Insufficiency Cohort (CRIC) Study Investigators include Lawrence J Appel, MD, MPH; Harold I Feldman, MD, MSCE; and John W Kusek, PhD.

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**ABSTRACT**

**Importance.** Elevated lipoprotein(a) [Lp(a)] levels are highly genetically determined and associated with increased cardiovascular disease (CVD) risk in the general population. While Lp(a) levels are also increased in persons with chronic kidney disease (CKD), its association with CVD events in CKD remains less clear.

**Objective.** To assess the relationship between variants at the *LPA* gene locus with Lp(a) level and renal function in persons with CKD, and determine the association between Lp(a) and myocardial infarction (MI) and death in this population.

**Design, Setting, and Participants.** The Chronic Renal Insufficiency Cohort (CRIC) Study is a multi-center prospective study of adults with CKD in the United States.

**Exposure.** Quartiles of baseline Lp(a) (mg/dL): <9.8 (Very Low), 9.8-26.0 (Low), 26.1-61.3 (High), and >61.3 (Very High).

**Main outcomes and measures.** A Cox proportional hazards model was used to compare quartiles of Lp(a) with risk for incident MI, death, and a composite of the two outcomes.

**Results.** In 3,635 CRIC participants with genotype data, carriers of either the rs10455872 or rs6930542 variant had a higher median Lp(a) level (mg/dL) compared to those without (73.3 versus 23.4, *P*-value < 0.0001 and 55.8 versus 21.7, *P*-value <0.0001, respectively). Median Lp(a) levels were also higher for lower ranges of estimated glomerular function rate (eGFR). There was no evidence of interaction between each single nucleotide polymorphism (SNP) and eGFR. In 3,744 participants (55% men, 59% non-White) with available baseline Lp(a), there were 315 MIs and 822 deaths over a median follow-up of 7.5 years. Low Lp(a) was associated with the lowest event rates of all quartiles. After adjusting for potential confounders, Very High Lp(a) was associated with increased risk of MI (hazard ratio [HR] 1.49, 95% confidence interval [95% CI] 1.05 – 2.11), death (HR 1.34, 95% CI 1.10-1.64), and the composite outcome (HR 1.32, 95% CI 1.10 – 1.59) compared to Low Lp(a). High Lp(a) also had an increased risk of MI (HR 1.46, 95% CI 1.04-2.06).

**Conclusions and Relevance.** Among adults with CKD, elevated Lp(a) is independently associated with MI and death. Future studies exploring pharmacologic Lp(a) reduction in CKD, as a means to reduce CVD in this high-risk population, are warranted.

## Introduction

Almost 15% of the adult population in the United States has chronic kidney disease (CKD)[1]. Studies indicate that more of these patients will die of cardiovascular diseases (CVD) than will progress to end-stage renal disease[2]. Renal dysfunction promotes a process of accelerated atherosclerosis



and abnormalities in lipoprotein morphology and metabolism that are unique to CKD[4]. The increased CVD risk in CKD is well-established

, and clinical practice guidelines[6] advise the use of statins in CKD to reduce this risk. Statins target low-density lipoprotein cholesterol (LDL-C) and have long been the cornerstone of atherosclerotic CVD prevention and management in the general population[7]. However, studies[8] have failed to show the same association between elevated LDL-C and increased risk for CVD in the setting of CKD as is seen in non-CKD persons. Herein lies a potential opportunity for greater CVD risk reduction in CKD by determining the role of other therapeutic targets, such as lipoprotein(a) [Lp(a)], which emerging agents, such as proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors

[9]

and antisense oligonucleotides

[10]

, have been shown to lower.

Lp(a) is a modified low-density lipoprotein covalently linked to apolipoprotein(a)[11,12]. Elevated Lp(a) is an independent and causal risk factor for atherosclerotic CVD in the general population

[13-15]

and is found in increased levels in CKD[16]. Plasma levels of Lp(a) are very highly genetically determined, primarily by variants at the *LPA* gene locus located on chromosome 6q26-q27

[17-19]

. Prior studies have shown that the rs10455872 and rs3798220 single nucleotide polymorphisms (SNPs) at this locus are strongly associated with Lp(a) level as well as increased risk for coronary artery disease

[20-22]

. In the Jackson Heart Study[23], the rs9457951 SNP was associated with a 25% increase in Lp(a) level per variant allele. Renal dysfunction is one of the few environmental factors that affects Lp(a) levels[24]. And, while studies have suggested that elevated Lp(a) levels are associated with the increased risk for atherosclerotic CVD events seen in those on hemodialysis

[13,25,26]

, the quantitative impact of Lp(a) on CVD risk in the population with non-dialysis dependent CKD remains less clear.

The primary objectives of this study, were to (1) determine the association between *LPA* variants and Lp(a) level in persons with CKD, (2) determine the association between baseline renal function and Lp(a) level in persons with CKD, (3) determine the interaction between these SNPs and renal function on Lp(a) level, and (4) relate baseline Lp(a) levels to myocardial infarction (MI) and death in this setting.

## Methods

### *Study Design*

The Chronic Renal Insufficiency Cohort (CRIC) Study is a prospective observational study established in 2001 by the National Institute of Diabetes, Digestive, and Kidney Diseases (NIDDK) to examine risk factors for progression of renal insufficiency and cardiovascular diseases in persons with mild- to moderate-CKD. The CRIC Study has been described extensively[27-30] and will be briefly summarized here.

### *Study Population*

A total of 3,939 participants were recruited for the CRIC Study from seven clinical centers located across the United States: Ann Arbor, MI; Baltimore, MD; Chicago, IL; Cleveland, OH; New Orleans, LA; Philadelphia, PA; and Oakland, CA. Participants aged 21-74 years were enrolled according to age-based estimated glomerular filtration rate (eGFR) inclusion criteria to limit the proportion of older individuals with age-related diminutions of GFR but otherwise non-progressive CKD. The eligible eGFR range was 20-70 mL/min per 1.73 $m^2$ for persons aged 21-44 years, 20-60 mL/min per 1.73 $m^2$ for persons aged 45-64 years, and 20-50 mL/min per 1.73 $m^2$ for persons aged 65-74 years. Exclusion criteria included: New York Heart Association class III or IV heart failure, cirrhosis, HIV/AIDS, multiple myeloma, renal carcinoma, polycystic kidney disease, recipient of organ transplant, previous dialysis, history of immunotherapy for renal disease or vasculitis, and history of chemotherapy. The institutional review board at each study site approved the study protocol. All participants provided written informed consent.

*Data Collection*

As has been previously described,[27,28] eligible participants completed an in-person baseline visit, during which sociodemographic characteristics, medical and family history, lifestyle behaviors, current medications, and anthropometric measurements were collected. In addition, blood samples were obtained and 24-hour urine sample collections were initiated. Participants returned annually for in-person follow-up visits with repeat blood samples taken. Plasma lipid and lipoproteins were measured on fasting blood samples prior to freezing using standard laboratory assays; Lp(a) was measured using a latex-enhanced immunoturbidimetric assay (Pointe Scientific, Canton, MI, USA). The eGFR was calculated using an equation derived from CRIC participants using serum creatinine and cystatin C, age, sex, and race



. Participants were contacted by telephone at six-month intervals between clinic visits to collect interim health status updates.

A total of 3,680 of the CRIC participants were genotyped using the Illumina HumanOmni1-quad Array Platform (Illumina, San Diego, CA, USA). The genotype data for 3,635 participants passed initial quality control metrics. The SNPs of interest, based on prior studies[20,23] that showed an association with

Lp(a) level in the general population, were: rs3798220, rs10455872, and rs9457951. The rs3798220 SNP, which is found mostly in Hispanics

[21]

, was monomorphic among the genotyped CRIC participants (less than 12% Hispanic), and was thus not further analyzed. The rs9457951 SNP was not located on the chip, so a proxy, rs6930542, determined to be in perfect linkage disequilibrium ($r^2 = 1$), was used in its place.

*Assessment of Outcomes*

Hospitalizations ascertained through participant self-report at the annual visits or through the six-month follow-up telephone interviews were confirmed by study personnel who reviewed medical records for the presence of International Classification of Diseases, Ninth or Tenth Edition (ICD-9/ICD-10) and Current Procedural Terminology (CPT) codes suggestive of atherosclerotic cardiovascular events. Medical encounters with codes suggestive of a CVD event were adjudicated by two physicians. Primary endpoints were defined as incident MI, death, and a composite of the two events. Deaths were ascertained from reports of next of kin, death certificates, obituaries, reviews of hospital records, and the Social Security Death Master File.

*Statistical Analysis*

All analyses were performed using Stata software, version 14 (StataCorp LP, College Station, TX, USA). Baseline characteristics were described using means with standard deviations (SD) or medians with interquartile ranges (IQR), when appropriate, for continuous variables, and with frequencies and percentages for categorical variables. Skewed variables were natural-log transformed for analyses. Group comparisons were conducted using Kruskal-Wallis tests for continuous variables and chi-square tests for categorical variables. Two-sided significance testing was used for all tests.

In participants who had undergone genotyping, the individual genotype information for the rs10455872 and rs6930542 SNPs were selected using PLINK v1.90 (https://www.cog-genomics.org/plink2). For each SNP, participants were stratified into two categories based on number of copies of the minor allele for the given SNP: zero versus at least one copy. A linear regression model, first unadjusted and then adjusted for age, gender, race/ethnicity, clinical site, systolic blood pressure, body mass index, tobacco use, diabetes mellitus, and statin use, was used to determine the association between minor allele copy number for each SNP separately with change in the log-transformed Lp(a) level. The models were repeated to determine the association between baseline eGFR as a two-category variable (above/below 45 mL/min/1.73m$^2$) with change in the log-transformed Lp(a) level. To test for interaction with CKD, an interaction term with the binary eGFR variable was included into the regression model for each SNP and a likelihood ratio test was used to determine the significance of the interaction.

Participants with available baseline Lp(a) levels were stratified into quartiles by baseline Lp(a) (Table 1). Cumulative event curves were constructed for each quartile for the composite outcome of MI or death using the Kaplan-Meier method. Crude event rates were determined from Kaplan-Meier rates and compared with the log-rank test. A Cox proportional hazards model was used for each outcome to determine cause-specific hazard ratios (HR) with associated confidence intervals (CIs) for each quartile of Lp(a). The quartile with the lowest event rate was used as the reference category. The proportional hazards assumption was met based on Schoenfeld residuals. Participants were censored either at time of

withdrawal from the study, time of last study visit (if they did not withdraw) or upon database lock in mid-2013, whichever occurred first.

A tiered approach was used to study the association between baseline Lp(a) level and CVD outcomes. Covariates were selected a priori on the basis of previously described risk factors for CVD development. First, the association was evaluated using an unadjusted, univariate analysis (Model 1). Model 2 adjusted for age, gender, race, and clinical site. The final model, Model 3, adjusted for the covariates in Model 2 as well as baseline systolic blood pressure, tobacco use, diabetes mellitus, high-density lipoprotein cholesterol (HDL-C), triglycerides, and statin use. In sensitivity analyses, the final model was additional adjusted for eGFR and 24-hour urine protein, however, this was not considered the final model because of likely overadjustment due to renal function being on the causal pathway for elevated Lp(a) levels. To explore whether there was effect modification, the final model (Model 3) for the composite outcome (MI or death) was repeated after stratifying by subgroups of age, gender, race/ethnicity, tobacco use, presence/absence of diabetes, baseline eGFR, and baseline 24-hour urine protein excretion, and tested for interaction by subgroup.

In further sensitivity analyses, participants who, at time of enrollment into the study, had a history of clinically significant cardiovascular disease, specifically MI, cardiac revascularization or a cerebrovascular event, were excluded from the survival analyses. Cerebrovascular events from the medical history were not further classified into subtypes, so all were excluded, given that over 80% of strokes would have been expected to be ischemic in etiology

[32,33]

.

**Results**

Of the 3,939 CRIC participants, the 3,744 participants with available baseline Lp(a) levels were divided into quartiles defined as follows: levels <9.8 mg/dL as “Very Low”, 9.8-26.0 mg/dL as “Low”, 26.1-61.3 mg/dL as “High”, and >61.3 mg/dL as “Very High.” Baseline characteristics for each quartile are described in Table 1. The mean age of the study cohort was 57.7 years; 54.7% were male, and 41.1% were Non-Hispanic White.

*Analyses of LPA Variants and Renal Function on Lp(a) Level*

There were 3,464 participants from the study cohort who also had genotype data for the rs10455872 SNP and 3,459 had genotype information for the rs6930542 SNP (Supplementary Table 1). There were 243 participants who had at least one minor allele of the rs10455872 SNP, 517 with at least one minor allele of the rs6930542 SNP, and seven with at least one minor allele of both SNPs. Seventy-seven percent of the rs10455872 variant carriers were non-Hispanic White, whereas 95% of the rs6930542 variant carriers were non-Hispanic Black. Lp(a) levels differed significantly with the presence of either SNP. The median Lp(a) level for carriers of the rs10455872 variant was 73.3 (IQR 54.7, 102.0) mg/dL compared to 23.4 (IQR 9.0, 54.4) mg/dL for non-carriers (*P*-value < 0.0001). Similarly, for the rs6930542 SNP, carriers of the variant had a higher Lp(a) level than non-carriers (55.8 [IQR 31.0, 91.2] mg/dL versus 21.7 [IQR 8.3, 53.5] mg/dL, *P*-value <0.0001). For the seven CRIC participants who had at least one minor allele copy of both SNPs, the median Lp(a) level was 102.9 (IQR 57.1, 147.0) mg/dL.

Table 2 summarizes the median Lp(a) levels for participants by baseline eGFR. Increasing levels of Lp(a) were observed for each level of decreasing eGFR (*P*-value = 0.0001). This pattern persisted

when stratifying by high versus low eGFR for each SNP (Supplementary Table 2); carriers of the rs10455872 variant with low eGFR had a higher median Lp(a) level than those with high eGFR (77.1 [IQR 58.8, 104.4] mg/dL) versus 67.9 [IQR 51.4, 94.5] mg/dL); *P*-value = 0.06) and carriers of the rs6930542 variant with low eGFR also had a higher median Lp(a) level than those with high eGFR (59.4 [IQR 33.9, 100.5] mg/dL versus 50.1 [IQR 26.0, 83.4] mg/dL; *P*-value = 0.02).

In the adjusted linear regression model, the presence of at least one minor allele copy of rs10455872 was associated with a 1.51 (95% CI 1.37-1.65) times higher log-transformed Lp(a) level (Supplementary Table 3). Using reverse log-transformation, this was equivalent to a 353% higher average Lp(a) level for those with at least one minor allele copy compared to the average Lp(a) level in non-carriers of the SNP. Similarly, the presence of at least one minor allele copy of rs6930542 was associated with a 0.43 (95% CI 0.32-0.55) times higher log-transformed Lp(a) level -- equivalent to a 54% higher average Lp(a) level for carriers of the variant. In analysis of the association of baseline renal function with baseline Lp(a) level, in the multivariable adjusted linear regression model, those with baseline eGFR values greater than the median (45 mL/min/1.73 $m^2$) had a 25% higher average baseline Lp(a) level compared to those with eGFR values less than the median. Testing for the interaction between each of the rs10455872 and rs6930542 SNPs and the binary eGFR variable was not significant (*P*-value = 0.57 and 0.50, respectively).

*Analyses of Lp(a) Levels and Clinical Outcomes*

Over a median follow-up period of 7.5 years, 315 participants had an MI and 822 participants died. For all events and the composite endpoint, event rates differed significantly amongst the quartiles of Lp(a) (Table 3). The second quartile, Low Lp(a), had the lowest event rate for all endpoints and was used as the reference quartile in the survival analyses. Kaplan-Meier time-to-event curves for the composite endpoint, showing time to incident MI or time to death for those who did not experience an MI, are shown in Figure 1. Hazard ratios with 95% CIs per quartile for each endpoint are summarized in Table 4 for the endpoints using unadjusted and adjusted models. After adjusting for baseline and CVD-related

covariates, High and Very High Lp(a) were significantly associated with MI, (HR 1.46, 95% CI 1.04-2.06, and HR 1.49, 95% 1.05-2.11, respectively). Very High Lp(a) was also associated with death with a HR of 1.34 (95% CI 1.10-1.64) and the composite outcome of MI or death, with a HR of 1.32 (95% CI 1.10-1.59).

We assessed for effect modification of the association between the quartiles of Lp(a) and the composite outcome of MI or death (Figure 3). Race/ethnicity and baseline 24-hour urine protein were found to be significant effect modifiers (*P*-value for interaction term < 0.05). When stratifying by different race/ethnicity categories, the HR for Very High Lp(a) compared to Low Lp(a) for non-Hispanic Whites was 1.70 (95% 1.24-2.34), for non-Hispanic Blacks was 1.24 (95% CI 0.95-1.61), and for Hispanics was 1.00 (95% CI 0.55-1.80). When stratifying by baseline 24-hour urine protein, the HR for Very High Lp(a) compared to Low Lp(a) was 1.69 (95% CI 1.29-2.20) for those with urine protein excretion < 0.5 g / 24h and 0.91 (95% CI 0.69-1.21) for those with urine protein excretion ≥ 0.5 g / 24 h.

In sensitivity analyses, 1045 participants with a history of MI, prior cardiac revascularization, or cerebrovascular event at time of enrollment were excluded, leaving 2,699 participants for the analyses. There were 152 incident MI cases and a total of 511 events (MI or death). Among these participants, Very High Lp(a) was associated with a 39% greater rate of both death (HR 1.39, 95% CI 1.05-1.85) and the composite outcome of MI or death (HR 1.39, 95% CI 1.07-1.80) compared to the second quartile of Lp(a).

**Discussion**

This study, a comprehensive analysis of data from the CRIC Study, evaluates the relationship between SNPs at the *LPA* locus and renal function with plasma Lp(a) level and offers substantive evidence for the association between elevated Lp(a) and adverse outcomes in the setting of CKD. This study showed that the rs10455872 variant and the rs6930542 variant (as a proxy for the rs9457951 SNP) are each independently associated with Lp(a) level in the CKD population, expanding on the findings of previous studies that have shown this association in non-CKD persons[20,23]. Findings from the analyses

also showed that with increasing levels of baseline renal insufficiency, as represented by decreasing baseline eGFRs, Lp(a) levels were progressively higher. Further, there appeared to be a compounding effect between the high risk variants and lower eGFR in those with CKD, resulting in higher Lp(a) levels for carriers compared to those with more preserved renal function.

This study was not powered to measure an association between each of the *LPA* variants and the outcomes. For the 243 carriers of the rs10455872 variant, there were only 69 composite events. The event rate (per 1000-person years) for carriers versus non-carriers (*P*-value = 0.45) of this variant was 44.7 (95% CI 35.5-56.6) versus 40.8 (95% CI 38.2-43.5). For the 517 carriers of the rs6930542, there were 156 total composite events, and the event rate for carriers versus non-carriers (*P*-value = 0.04) was 48.0 (95% CI 41.0-56.2) versus 39.9 (95% CI 37.2-42.8). In a 2009 study, by meta-analyzing genotype data from multiple sources, Clarke et al[20] were able to show that with a genotype score involving both the rs10455872 and rs3798220 variants, the odds of coronary disease were 1.5 times higher with the presence of one variant and over 2.5 times higher with the presence of two or more variants. In contrast, while the rs9457951 SNP, for which we used rs6930542 as a proxy, was shown to be associated with elevated Lp(a) in the Jackson Heart Study[23], the study investigators did not find an association with incident coronary heart disease in replication analyses using the Atherosclerosis Risk in Communities (ARIC) Study.

While other studies had shown that Lp(a) levels are elevated in the setting of CKD [11,16], published data on the relationship between Lp(a) and CVD outcomes in CKD are both limited and variable in their conclusions. In a study published in 2005, Shlipak, et al.[34] evaluated risk factors for death due to CVD in 5,808 participants from the Cardiovascular Health Study, stratified by presence of CKD and followed for a mean of 8.6 years. In the 1,249 participants with CKD, the study authors found that the highest quartile of Lp(a), compared to the lower three quartiles, was not significantly associated with cardiovascular mortality (HR 1.20, 95% CI 0.93-1.54). In a 2015 study from Japan, Konishi, et al.[35] reported on the association between Lp(a) level and poor outcomes (death and/or acute coronary syndrome) in 904 CKD patients who underwent percutaneous coronary intervention. The study authors found an increased risk in those with Lp(a) levels above the median compared to those below (HR 1.35, 95% CI 1.01-1.82). Both of

these studies are limited in their generalizability. The CKD patients in the Cardiovascular Health Study were much older than the CRIC population (mean age 75 versus 57.7 years). And, Konishi, et al. studied CKD patients undergoing invasive management for coronary artery disease at a single institution in Japan.

Results from this study indicate a strong and substantial increase in events and outcomes in CKD with the presence of elevated Lp(a). After using a multivariable-adjusted model, the upper two quartiles of the CRIC cohort who had an Lp(a) level above the median (i.e., >26 mg/dL) experienced a 46% and 49% higher rate of MI, respectively, compared to those with a lower Lp(a) level. And, those in the uppermost quartile of Lp(a) level had a 34% higher rate of death. Further, the association of the highest quartile of Lp(a) with incident MI or death remained significant after excluding those with prevalent disease, strengthening the argument that elevated Lp(a) is a contributing factor to the development of clinically significant atherosclerosis in the setting of CKD. In subgroup analyses, the association between elevated Lp(a) and clinical outcomes seemed to be the strongest for non-Hispanic Whites as well as those CKD persons with lower levels of proteinuria.

In the CRIC population, it was the second quartile of Lp(a), and not the first, that experienced the lowest event rates. Notably, those in the lowest quartile, with Lp(a) levels <9.8 mg/dL, had the highest baseline median triglyceride levels (142.0 [IQR 97.0, 221.0] mg/dL). It is conceivable that there is a subgroup with very low Lp(a) levels for whom elevated triglyceride levels served as the driving factor for the higher event rates observed. This should be further explored in future studies of persons with CKD and/or those with very low levels of Lp(a).

This study has several strengths. The CRIC Study cohort is a large diverse group of persons with a range of renal dysfunction at baseline. The study is also notable for having a low participant dropout rate (< 2% per year) and lengthy follow-up period. The detailed collection of baseline and covariate information allowed for robust multivariate analyses and subgroup analyses. Furthermore, the availability of genotype data on the CRIC participants is a unique resource to examine genetic risk factors in the CKD

population. The large number of both non-Hispanic Whites and Blacks allowed us to study two SNPs at the *LPA* locus that appear in vastly different frequencies in these races

[21,23]

.

This study is not without limitations. First, the cross-sectional analysis of baseline data in this study suggests that with increasing levels of renal insufficiency there are increasing levels of Lp(a). A longitudinal analysis of Lp(a) levels followed over time in those with worsening renal function may offer more insight into the biology of the Lp(a) elevation seen in CKD. Second, while results suggest an additive effect of genetic variants at the *LPA* locus and renal dysfunction on Lp(a) level, future studies evaluating the impact of these SNPs and renal function in a cohort of persons with and without CKD could answer the question of what the relative contribution of renal dysfunction to Lp(a) level is and whether the strength of the association between elevated Lp(a) and CVD differs amongst these two groups. Third, while the association between elevated Lp(a) and all-cause mortality found in this study is likely driven by a high proportion of CVD-related deaths in CKD

[36,37]

, cause of death was not known at the time of this study. Fourth, renal dysfunction may drive CVD risk through pathways

[38]

other than Lp(a) elevation. When the hazards models were additionally adjusted for eGFR and urine protein, High and Very High Lp(a) remained significantly associated with MI (HR 1.45, 95% CI 1.02-2.05 and HR 1.43, 95% CI 1.00-2.03, respectively) when compared to Low Lp(a). However, the inclusion of these parameters may represent an overadjustment because renal dysfunction is likely on the causal pathway for increased Lp(a).

The high burden of CVD in the CKD-population, and the unique nature of dyslipidemia and atherosclerosis in this setting[4], demands novel avenues beyond statins to reduce the risk for MI and other

atherosclerotic diseases in this population. This study offers convincing evidence that the elevated Lp(a) seen in CKD could thus be an effective target to reduce risk for CVD events and death in this high risk population. Studies have suggested that lower Lp(a) levels are associated with reduced CVD risk among the general population. In genomic analyses using several large data sources, Emdin et al.



showed that genetically lowered levels of Lp(a) are associated with a reduction in not only coronary disease, but also peripheral vascular disease, stroke, and aortic stenosis. Future studies evaluating Lp(a) reduction, such as with PCSK9 inhibitors, antisense oligonucleotides or other emerging therapies, in persons with CKD are warranted.

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