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

## Findings From the CRIC Study (Chronic Renal Insufficiency Cohort)

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***Objective***—To investigate the effect of *LPA* gene variants and renal function on lipoprotein(a) [Lp(a)] levels in people with chronic kidney disease and determine the association between elevated Lp(a) and myocardial infarction and death in this setting.

***Approach and Results***—The CRIC Study (Chronic Renal Insufficiency Cohort) is an ongoing prospective study of 3939 participants with chronic kidney disease. In 3635 CRIC participants with genotype data, carriers of the rs10455872 or rs6930542 variants had a higher median Lp(a) level (mg/dL) compared with noncarriers (73 versus 23; $P<0.001$ and 56 versus 22; $P<0.001$, respectively). The 3744 participants (55% male and 41% non-Hispanic White) with available baseline Lp(a) levels were stratified into quartiles of baseline Lp(a) (mg/dL): <9.8, 9.8 to 26.0, 26.1 to 61.3, and >61.3. There were 315 myocardial infarctions and 822 deaths during a median follow-up of 7.5 years. The second quartile had the lowest event rate. After adjusting for potential confounders and using a Cox proportional hazards model, the highest quartile of Lp(a) was associated with increased risk of myocardial infarction (hazard ratio, 1.49; 95% confidence interval, 1.05–2.11), death (hazard ratio, 1.28; 95% confidence interval, 1.05–1.57), and the composite outcome (hazard ratio, 1.29; 95% confidence interval, 1.07–1.56) compared with the second quartile of Lp(a).

***Conclusions***—Among adults with chronic kidney disease, elevated Lp(a) is independently associated with myocardial infarction and death. Future studies exploring pharmacological Lp(a) reduction in this population are warranted.

***Visual Overview***—An online visual overview is available for this article. (***Arterioscler Thromb Vasc Biol*. 2017;37: 1971-1978. DOI: 10.1161/ATVBAHA.117.309920.)**

**Key Words:** chronic kidney disease ■ genotype ■ lipoprotein(a) ■ myocardial infarction



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[3] and abnormalities in lipoprotein morphology and metabolism that are unique to CKD.[4] The increased CVD risk in CKD is well established,[5] and clinical practice guidelines[6] advise using statins to reduce this risk. Statins target low-density lipoprotein cholesterol and have long been the cornerstone of atherosclerotic CVD prevention in the general population.[7] However, in people with CKD, there still remains a substantial risk for CVD even after treatment with statins.[8] Further, studies have failed to show the same association between

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| Nonstandard Abbreviations and Acronyms | |
|---|---|
| CI | confidence interval |
| CKD | chronic kidney disease |
| CRIC | Chronic Renal Insufficiency Cohort |
| CVD | cardiovascular disease |
| eGFR | estimated glomerular filtration rate |
| HR | hazard ratio |
| IQR | interquartile range |
| Lp(a) | lipoprotein(a) |
| MI | myocardial infarction |
| PCSK9 | proprotein convertase subtilisin/kexin type 9 |
| SNP | single nucleotide polymorphism |

elevated low-density lipoprotein cholesterol and increased risk for CVD in the setting of CKD[9] as is seen in non-CKD people. Herein lies a potential opportunity for greater CVD risk reduction in CKD by determining the role of therapeutic targets other than low-density lipoprotein cholesterol.

Lipoprotein(a) [Lp(a)] is a modified low-density lipoprotein particle covalently linked to apolipoprotein(a).[10,11] Elevated Lp(a) is an independent and causal risk factor for atherosclerotic CVD in the general population[12–14] and is found in increased levels in CKD.[15] Plasma levels of Lp(a) are highly genetically determined, primarily by variants at the *LPA* gene locus located on chromosome 6q26-q27.[16–18] 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.[19–21] In the Jackson Heart Study,[22] another SNP at the *LPA* locus, rs9457951, 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.[23] 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,[12,24,25] the quantitative impact of Lp(a) on CVD risk in the population with nondialysis-dependent CKD remains less clear. Determining the role of elevated Lp(a) in this setting may guide the future direction of CVD prevention in CKD as emerging agents, such as PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitors[26] and apolipoprotein(a) antisense oligonucleotides,[27] have been shown to lower Lp(a).

The primary objectives of this study were to (1) determine the association between *LPA* variants and Lp(a) level in people with CKD, (2) determine the association between baseline renal function and Lp(a) level in people 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.

## Materials and Methods

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

## Results

Of the 3939 CRIC (Chronic Renal Insufficiency Cohort) participants, the 3744 participants with available baseline Lp(a) levels were divided into quartiles: the first quartile was Lp(a) levels <9.8 mg/dL, the second quartile was Lp(a) levels of 9.8 to 26.0 mg/dL, the third quartile was Lp(a) levels of 26.1 to 61.3 mg/dL, and the fourth quartile was Lp(a) levels >61.3 mg/dL. Baseline characteristics for each quartile are described in Table 1. The mean age of the study cohort was 58 years; 54.7% were male, and 41.1% were non-Hispanic White.

### Association of LPA Variants and Renal Function With Lp(a) Level

There were 3464 participants from the study cohort who also had genotype data for the rs10455872 SNP and 3459 participants with genotype data for the rs6930542 SNP, which was used as a proxy for the rs9457951 SNP (Table I in the online-only Data Supplement). Variants of the rs3798220 SNP were not found in the CRIC population. There were 243 carriers of the rs10455872 SNP, 517 carriers of the rs6930542 SNP, and 7 with at least 1 minor allele of both SNPs. Lp(a) levels differed significantly with the presence of either SNP. The median Lp(a) level for carriers of the rs10455872 variant was 73 (interquartile range [IQR], 55–102) mg/dL compared with 23 (IQR, 9–54) mg/dL for noncarriers ($P$<0.001). Similarly, for the rs6930542 SNP, carriers had a higher Lp(a) level than noncarriers (56 [IQR, 31–91] mg/dL versus 22 [IQR, 8–54] mg/dL; $P$<0.001). For the 7 participants who were carriers of both SNPs, the median Lp(a) level was 103 (IQR, 57–147) mg/dL.

Table 2 summarizes Lp(a) levels for participants by baseline estimated glomerular filtration rate (eGFR). Increasing levels of Lp(a) were observed for each level of lower eGFR ($P$<0.001). This pattern persisted when stratifying by eGFR above/below the median 45 mL/min per 1.73 m$^2$ for each *LPA* SNP (Figure 1; Table II in the online-only Data Supplement); rs10455872 variant carriers with low eGFR had a higher median Lp(a) level than those with high eGFR (77 [IQR, 59–104] mg/dL versus 68 [IQR, 51–95] mg/dL; $P$=0.06) and rs6930542 variant carriers with low eGFR also had a higher median Lp(a) level than those with high eGFR (59 [IQR, 34–101] mg/dL versus 50 [IQR, 26–83] mg/dL; $P$=0.02).

In the adjusted linear regression model, the presence of at least 1 minor allele copy of rs10455872 was associated with a 1.51 (95% confidence interval [CI], 1.37–1.65) times higher log-transformed Lp(a) level (Table III in the online-only Data Supplement). Using reverse log transformation, this is equivalent to a 353% higher average Lp(a) level for carriers compared with noncarriers of the SNP. Similarly, carriers of the rs6930542 variant were associated with a 0.43 (95% CI, 0.32–0.55) times higher log-transformed Lp(a) level than noncarriers—equivalent to a 54% higher average Lp(a). In analysis of the association of baseline renal function with baseline Lp(a) level, those with eGFR values lower than 45 mL/min per 1.73 m$^2$ had a 16% higher average Lp(a) level compared with those with higher eGFR, after adjusting for covariates. Testing for the interaction between each of the rs10455872 and rs6930542 SNPs and the binary eGFR variable was not significant ($P$=0.57 and 0.50, respectively).

### Association of Lp(a) Levels With Clinical Outcomes

Over a median follow-up period of 7.5 years, 315 participants experienced an MI, and there was a total of 822 deaths. For

**Table 1. Baseline Characteristics of CRIC Study Participants**

| Characteristics | Lipoprotein(a) | | | | *P* Value |
|---|---|---|---|---|---|
| | Quartile 1, <9.8 mg/dL (n=936) | Quartile 2, 9.8–26.0 mg/dL (n=940) | Quartile 3, 26.1–61.3 mg/dL (n=935) | Quartile 4, >61.3 mg/dL (n=933) | |
| Age, mean (SD), y | 57 (11) | 57 (11) | 57 (11) | 58 (11) | 0.14 |
| Men, No. (%) | 565 (60.4) | 530 (56.4) | 492 (52.6) | 460 (49.3) | <0.001 |
| Race/ethnicity, No. (%) | | | | | |
| Non-Hispanic White | 596 (63.7) | 436 (46.4) | 266 (28.4) | 242 (25.9) | <0.001 |
| Non-Hispanic Black | 126 (13.5) | 331 (35.2) | 556 (59.5) | 595 (63.8) | <0.001 |
| Hispanic | 149 (15.9) | 130 (13.8) | 94 (10.1) | 74 (7.9) | <0.001 |
| Other | 65 (6.9) | 43 (4.6) | 19 (2.0) | 22 (2.4) | <0.001 |
| High school graduate, No. (%) | 786 (84.0) | 765 (81.5) | 712 (76.2) | 703 (75.4) | <0.001 |
| Medical history | | | | | |
| Current smoker, No. (%) | 94 (10.0) | 112 (11.9) | 138 (14.8) | 150 (16.1) | <0.001 |
| >100 cigarettes in lifetime, No. (%) | 515 (55.0) | 486 (51.7) | 513 (54.9) | 540 (57.9) | 0.07 |
| Current alcohol use, No. (%) | 638 (68.2) | 585 (62.2) | 560 (59.9) | 563 (60.3) | 0.001 |
| Prior MI/revascularization, No. (%) | 199 (21.3) | 195 (20.7) | 176 (18.8) | 249 (26.7) | <0.001 |
| Prior stroke, No. (%) | 71 (7.6) | 78 (8.3) | 101 (10.8) | 125 (13.4) | <0.001 |
| Hypertension, No. (%) | 769 (82.2) | 802 (85.3) | 808 (86.4) | 846 (90.7) | <0.001 |
| Diabetes mellitus, No. (%) | 448 (47.9) | 445 (47.3) | 444 (47.5) | 483 (51.8) | 0.17 |
| Statin use, No. (%) | 487 (52.1) | 491 (52.6) | 493 (53.1) | 574 (62.3) | <0.001 |
| Anthropometric measurements | | | | | |
| Systolic BP, mean (SD), mm Hg | 125 (20) | 127 (21) | 130 (23) | 132 (24) | <0.001 |
| Diastolic BP, mean (SD), mm Hg | 71 (12) | 71 (13) | 72 (13) | 72 (13) | 0.20 |
| BMI, mean (SD), kg/m$^2$* | 31.5 (7.3) | 32.0 (7.9) | 32.5 (7.7) | 32.5 (8.5) | 0.01 |
| Waist circumference, mean (SD), cm | 105.3 (17.1) | 105.9 (17.5) | 106.7 (17.8) | 105.8 (18.1) | 0.46 |
| HbA1c, mean (SD), % | 6.6 (1.4) | 6.6 (1.5) | 6.6 (1.5) | 6.9 (1.7) | <0.001 |
| Plasma lipids | | | | | |
| Total cholesterol, mean (SD), mg/dL | 178 (44) | 180 (42) | 183 (45) | 194 (49) | <0.001 |
| LDL-C, mean (SD), mg/dL | 95 (33) | 100 (34) | 104 (36) | 114 (37) | <0.001 |
| VLDL-C, median (IQR), mg/dL | 30 (19–47) | 28 (17–43) | 26 (16–40) | 25 (15–37) | <0.001 |
| HDL-C, mean (SD), mg/dL | 46 (15) | 47 (16) | 47 (14) | 50 (16) | <0.001 |
| Triglycerides, median (IQR), mg/dL | 142 (97–221) | 127 (88–190) | 123 (86–173) | 120 (86–166) | <0.001 |
| Kidney function measures | | | | | |
| Serum creatinine, mean (SD), mg/dL | 1.71 (0.54) | 1.81 (0.61) | 1.90 (0.67) | 1.96 (0.73) | <0.001 |
| Serum cystatin C, median (IQR), mg/L | 1.37 (1.07–1.74) | 1.38 (1.11–1.81) | 1.44 (1.10–1.86) | 1.49 (1.17–1.92) | <0.001 |
| eGFR, mean (SD), mL/min/1.73 m$^2$ | 47.2 (16.9) | 45.6 (16.9) | 44.3 (17.1) | 42.1 (16.0) | <0.001 |
| Urine protein/24 hour, median (IQR), g | 0.15 (0.07–0.71) | 0.17 (0.07–0.80) | 0.22 (0.07–0.98) | 0.23 (0.08–1.17) | 0.002 |

BMI indicates body mass index; BP, blood pressure; CRIC, Chronic Renal Insufficiency Cohort; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; SD, standard deviation; VLDL-C, very low–density lipoprotein cholesterol.

*Calculated as weight in kilograms divided by height in meters squared.



all events and the composite end point, event rates differed significantly among the quartiles of Lp(a) (Table 3). The second quartile had the lowest event rate for all end points and was used as the reference quartile in the survival analyses. Kaplan–Meier time-to-event curves for the composite end point (MI or death) are shown in Figure 2. Hazard ratios (HRs) with 95% CIs per quartile for each end point are summarized in Table 4. After adjusting for covariates, the third and fourth quartiles of Lp(a) were significantly associated with MI (HR, 1.45; 95% CI, 1.03–2.05; *P*=0.03 and HR, 1.49;

**Table 2. Median Lp(a) Levels for Study Participants by Baseline Renal Function**

| | eGFR, mL/min per 1.73 m$^2$ | | | | | | |
|---|---|---|---|---|---|---|---|
| | ≥90 (n=51) | 60 to <90 (n=605) | 45 to <60 (n=1032) | 30 to <45 (n=1293) | 15 to <30 (n=752) | <15 (n=11) | *P* Value |
| Lp(a), median (IQR), mg/dL | 20 (7–62) | 21 (8–47) | 24 (9–56) | 27 (10–66) | 32 (13–71) | 57 (29–85) | <0.001 |

eGFR indicates estimated glomerular filtration rate; IQR, interquartile range; and Lp(a), lipoprotein(a).

95% CI, 1.05–2.11; *P*=0.03 respectively). The fourth quartile was also associated with death with a HR of 1.28 (95% CI, 1.05–1.57; *P*=0.02) and the composite outcome, with a HR of 1.29 (95% CI, 1.07–1.56; *P*=0.01).

Proteinuria was found to be a significant effect modifier on the association between elevated Lp(a) and the composite outcome of MI or death (*P* value for interaction =0.02; Figure I in the online-only Data Supplement). When stratifying by baseline 24-hour urine protein excretion, the HR for the fourth quartile was 1.62 (95% CI, 1.24–2.12) for those with urine protein <0.5 g/24 h and 0.88 (95% CI, 0.66–1.17) for those with urine protein ≥0.5 g/24 h.

In sensitivity analyses, 1045 participants with a history of CVD were excluded, leaving 2699 participants for analyses. There were 152 incident MI cases and a total of 511 events (incident MI or death). Among this subset of participants, elevated Lp(a) was not found to be significantly associated with incident MI (HR, 1.46; 95% CI, 0.88–2.41; *P*=0.14 for the fourth quartile compared with the second quartile). However, the highest quartile of Lp(a) was associated with a 33% higher rate of death (HR, 1.33; 95% CI, 1.00–1.77; *P*=0.049) and a 36% higher rate of the composite outcome (HR, 1.36; 95% CI, 1.04–1.76; *P*=0.02) compared with the second quartile.

## Discussion

This 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 a large and diverse cohort of people with 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 this population with CKD, expanding on the findings of previous studies that have shown this association in the non-CKD setting.[19,22] Findings from the analyses also showed that with increasing severity of renal disease at baseline, Lp(a) levels were progressively higher. There appeared to be a compounding effect between the variants and renal function, resulting in higher Lp(a) levels for *LPA* variant carriers with more progressive renal disease compared with those with more preserved renal function.

The median Lp(a) level of 126 634 participants in a 2009 meta-analysis by the Emerging Risk Factors Collaboration[14] was 12.6 mg/dL (IQR, 4.9–32.1 mg/dL), revealing the general range of Lp(a) levels in the wider population. In comparison, the median level in the CRIC population was 26 mg/dL (IQR, 9.8–61.3 mg/dL). The study authors of the meta-analysis noted a 2-fold higher median level in Blacks compared with Whites, but the median Lp(a) level of 14.1 mg/dL (IQR, 6.4–37.3 mg/dL) among the non-Hispanic Whites (n=1540) in the CRIC population is still higher than that for the combined population in the meta-analysis. In the MESA (Multi-Ethnic Study of Atherosclerosis),[28] a United States–based cohort of over 6000 adults free from CVD at baseline, the reported median Lp(a) level in the 1347 Black participants was 35.1 mg/dL (IQR, 20.4–61.6 mg/dL), which is lower than the median of 45.4 mg/dL (IQR, 23.8–79.3 mg/dL) in the 1608 non-Hispanic Blacks in the CRIC population. It is unclear why Lp(a) levels are elevated in the setting of CKD but is thought to be because of decreased renal clearance.[15] In the analysis of 66 renal transplant recipients and 31 hemodialysis patients at one institution, Rosas et al[29] found that Lp(a) levels did not change after initiation of hemodialysis but decreased significantly after renal transplant.

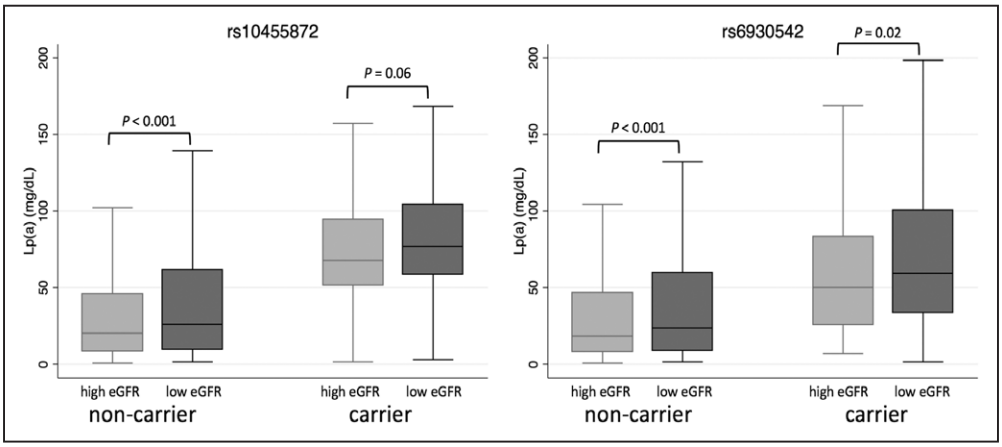


**Figure 1.** Lipoprotein(a) [Lp(a)] levels for CRIC Study (Chronic Renal Insufficiency Cohort) participants by *LPA* single nucleotide polymorphism (SNP) carrier status and baseline estimated glomerular filtration rate (eGFR). Boxplots showing the median and interquartile ranges of Lp(a) levels with outside values excluded. High eGFR indicates eGFR ≥45 mL/min per 1.73 m$^2$, low eGFR indicates eGFR <45 mL/min per 1.73 m$^2$.

**Table 3. Event Rates of Study Participants for Myocardial Infarction, Death, and a Composite of Both Outcomes**

| | | Lipoprotein(a) | | | | |
|---|---|---|---|---|---|---|
| | | Quartile 1, <9.8 mg/dL (n=936) | Quartile 2, 9.8–26.0 mg/dL (n=940) | Quartile 3, 26.1–61.3 mg/dL (n=935) | Quartile 4, >61.3 mg/dL (n=933) | *P* Value |
| Myocardial infarction | Participants, no. | 78 | 57 | 87 | 93 | |
| | Event rate* | 12.8 (10.3–16.0) | 9.4 (7.3–12.2) | 14.6 (11.8–18.0) | 16.1 (13.2–19.7) | 0.01 |
| Death | Participants, no. | 185 | 176 | 201 | 260 | |
| | Event rate* | 28.1 (24.4–32.5) | 26.7 (23.0–31.0) | 30.9 (26.9–35.5) | 41.2 (36.4–46.5) | <0.001 |
| Myocardial infarction or death | Participants, no. | 230 | 204 | 242 | 304 | |
| | Event rate* | 37.9 (33.3–43.1) | 33.7 (29.4–38.6) | 40.6 (35.8–46.0) | 52.7 (47.1–58.9) | <0.001 |

*Event rate per 1000 person-years.

While other studies have also shown that Lp(a) levels are elevated in the setting of CKD,[10,15] 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[30] evaluated risk factors for death caused by CVD in 5808 participants from the Cardiovascular Health Study followed for a mean of 8.6 years. In the 1249 participants with CKD, the study authors found that the highest quartile of Lp(a), compared with the lower 3 quartiles, was not significantly associated with cardiovascular mortality (HR, 1.20; 95% CI, 0.93–1.54). Notably, the CKD patients were much older than the CRIC population (mean age 75 versus 58 years). In a 2015 study from Japan, Konishi et al[31] reported on the association between Lp(a) level and poor outcomes (death and acute coronary syndrome) in 904 CKD patients who underwent percutaneous coronary intervention at a single institution in Japan. The study authors found an increased risk for outcomes in those with Lp(a) levels above the median compared with those below (HR, 1.35; 95% CI, 1.01–1.82).

Results from our 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 2 quartiles of the CRIC cohort (with Lp(a) >26 mg/dL) experienced a 45% and 49% higher risk of MI, respectively, compared with those with a lower Lp(a) level. And, those in the uppermost quartile of Lp(a) level had a 28% higher risk of death. The association between elevated Lp(a) and outcomes seen in the CRIC population seem to be higher than the associations reported in the wider population. In the meta-analysis by the Emerging Risk Factors Collaboration,[14] the study authors reported an adjusted summary relative risk of 1.27 (95% CI, 1.17–1.38) for coronary heart disease for those in the top third of Lp(a) levels compared with those in the bottom third.

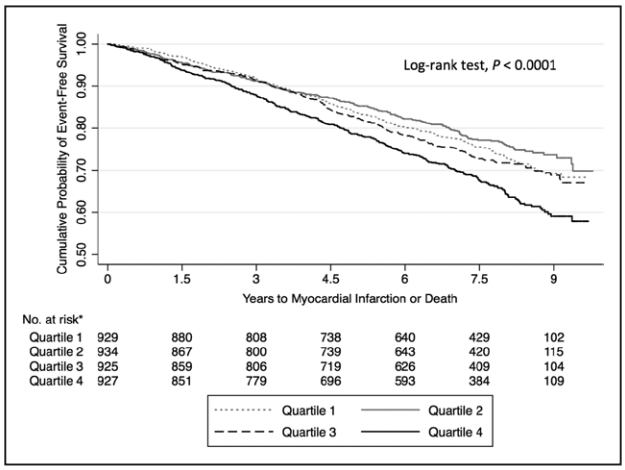


**Figure 2.** Event-free survival curves for CRIC Study (Chronic Renal Insufficiency Cohort) participants by lipoprotein(a) [Lp(a)] quartiles. Study participants in the highest quartile of Lp(a) experienced a higher rate of myocardial infarction or death than those in lower quartiles of Lp(a). *Participants who withdrew immediately after baseline visit are not included.

This study was not powered to measure an association between 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 noncarriers (*P*=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 noncarriers (*P*=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[19] showed that with a genotype score involving both the rs10455872 and rs3798220 variants, the odds of coronary disease were 1.5× higher with the presence of one variant and over 2.5× higher with the presence of ≥2 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,[22] study investigators did not find an association with incident coronary heart disease in replication analyses using the ARIC Study (Atherosclerosis Risk in Communities).

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 (Lp(a) <9.8 mg/dL) had the highest baseline triglyceride levels (142 [IQR, 97–221] mg/dL). It is conceivable that there is a subgroup with 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 people with CKD and those with low levels of Lp(a).

## Strengths and Limitations

This study has several strengths. The CRIC Study cohort is a large diverse group of people with a range of renal

**Table 4. Association Between Lipoprotein(a) Level and Clinical Outcomes**

| | Model 1* | | Model 2† | | Model 3‡ | |
|---|---|---|---|---|---|---|
| | HR (95% CI) | *P* Value | HR (95% CI) | *P* Value | HR (95% CI) | *P* Value |
| Myocardial infarction | | | | | | |
| Quartile 1 | 1.36 (0.97–1.92) | 0.07 | 1.34 (0.95–1.90) | 0.10 | 1.27 (0.90–1.81) | 0.18 |
| Quartile 2 | 1 (Reference) | | 1 (Reference) | | 1 (Reference) | |
| Quartile 3 | 1.55 (1.11–2.17) | 0.01 | 1.48 (1.05–2.08) | 0.02 | 1.45 (1.03–2.05) | 0.03 |
| Quartile 4 | 1.71 (1.23–2.38) | 0.001 | 1.58 (1.12–2.21) | 0.01 | 1.49 (1.05–2.11) | 0.03 |
| Death | | | | | | |
| Quartile 1 | 1.05 (0.86–1.30) | 0.62 | 1.07 (0.87–1.32) | 0.51 | 1.03 (0.84–1.28) | 0.75 |
| Quartile 2 | 1 (Reference) | | 1 (Reference) | | 1 (Reference) | |
| Quartile 3 | 1.16 (0.95–1.42) | 0.15 | 1.08 (0.87–1.32) | 0.50 | 1.04 (0.84–1.28) | 0.74 |
| Quartile 4 | 1.56 (1.28–1.88) | <0.001 | 1.40 (1.15–1.70) | 0.001 | 1.28 (1.05–1.57) | 0.02 |
| Myocardial infarction or death | | | | | | |
| Quartile 1 | 1.13 (0.93–1.36) | 0.22 | 1.15 (0.95–1.39) | 0.16 | 1.10 (0.91–1.34) | 0.32 |
| Quartile 2 | 1 (Reference) | | 1 (Reference) | | 1 (Reference) | |
| Quartile 3 | 1.21 (1.00–1.46) | 0.047 | 1.13 (0.93–1.36) | 0.22 | 1.08 (0.89–1.32) | 0.41 |
| Quartile 4 | 1.57 (1.32–1.88) | <0.001 | 1.40 (1.16–1.68) | <0.001 | 1.29 (1.07–1.56) | 0.01 |

Lp(a) quartiles defined as follows (in mg/dL): <9.8 as Quartile 1, 9.8–26.0 as the Quartile 2, 26.1–61.3 as the Quartile 3, and >61.3 as the Quartile 4. CI indicates confidence interval; HR, hazard ratio; and Lp(a), lipoprotein(a).

*Model 1 is an unadjusted Cox proportional hazards model.

†Model 2 adjusts for age, sex, race/ethnicity, and clinical site.

‡Model 3 adjusts for the above and education level, tobacco use, diabetes mellitus, history of prior cardiovascular disease, systolic blood pressure, body mass index, statin use, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides.



dysfunction at baseline. There is a low participant dropout rate (<2% per year) and lengthy follow-up period. The detailed collection of baseline 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 Whites and Blacks allowed an analysis of 2 *LPA* SNPs that appear in vastly different frequencies in these races. Carriers of the rs10455872 SNP, which has been primarily found in Whites with European ancestry, with studies estimating that this variant is present in 7% to 15% of the general population of Europeans,[19,32] were 77% non-Hispanic White in this study. Similarly, carriers of the rs6930542 SNP were 95% non-Hispanic Black in the CRIC population, consistent with studies that have shown that the rs9457951 SNP is primarily associated with Blacks with a reported minor allele frequency of 0.19 in the Jackson Heart Study.[22]

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), but causality cannot be concluded from this analysis. Repeated measurements of Lp(a) were not collected in the CRIC study. A longitudinal analysis of Lp(a) levels over time in those with worsening renal function may offer insight into the biology of the Lp(a) elevation seen in CKD. Second, while results suggest an additive effect of *LPA* variants and renal dysfunction on Lp(a) level, future studies evaluating the impact of these SNPs and renal function in a cohort of people with and without CKD could determine the relative contribution of renal dysfunction to Lp(a) level and whether the strength of the association between elevated Lp(a) and CVD differs among these 2 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,[33,34] cause of death was not known at the time of this study. Fourth, renal dysfunction may drive CVD risk through pathways[35] other than Lp(a) elevation. When the hazards model was additionally adjusted for eGFR and urine protein excretion, the third quartile of Lp(a) remained significantly associated with MI (HR, 1.43; 95% CI, 1.01–2.03; $P$=0.046); all other associations were not statistically significant. However, the inclusion of these parameters may represent an overadjustment because renal impairment is likely on the causal pathway for the elevated Lp(a) seen in CKD.

## Conclusions

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. In genomic analyses using several large data sources,[36] genetically lower levels of Lp(a) have been shown to be associated with a reduction in not only coronary disease but also in peripheral vascular disease, stroke, and aortic stenosis. This study offers convincing evidence that the elevated Lp(a) seen in CKD could, thus, be an effective target to reduce risk for

CVD and these associated disorders in this high-risk population. Future studies evaluating Lp(a) reduction, such as with PCSK9 inhibitors, apolipoprotein(a) antisense oligonucleotides, or other emerging therapeutics, in people with CKD are warranted.

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## Highlights

- In this cohort of people with chronic kidney disease, participants with lower baseline renal function had higher levels of lipoprotein(a) compared with those with more preserved renal function, including among carriers of known genetic variants that affect lipoprotein(a) level.
- Study participants who had the highest baseline levels of lipoprotein(a) were at the highest risk for myocardial infarction and death.
- Clinical studies of therapies that target lipoprotein(a) are warranted in people with chronic kidney disease in an attempt to reduce the burden of cardiovascular disease in this high-risk population.