

Relation of Serum Lipids and Lipoproteins with Progression of CKD: The CRIC Study

Mahboob Rahman,* Wei Yang,[†] Sanjeev Akkina,[‡] Arnold Alper,[§] Amanda Hyre Anderson,[†] Lawrence J. Appel,^{||} Jiang He,[§] Dominic S. Raj,[¶] Jeffrey Schelling,^{**} Louise Strauss,^{††} Valerie Teal,[‡] and Daniel J. Rader,^{**} for the CRIC Study Investigators

Abstract

Background and objectives Hyperlipidemia is common in patients with CKD. The objective of this study was to evaluate whether measures of plasma lipids and lipoproteins predict progression of kidney disease in patients with CKD.

Design, setting, participants, & measurements Prospective cohort study in adults ($n=3939$) with CKD aged 21–74 years recruited between 2003 and 2008 and followed for a median of 4.1 years. At baseline, total cholesterol, triglycerides, very-low-density lipoprotein cholesterol (VLDL-C), LDL cholesterol (LDL-C), HDL cholesterol (HDL-C), apoA-I, apoB, and lipoprotein(a) [Lp(a)] were measured. The outcomes were composite end point of ESRD or 50% decline in eGFR from baseline (rate of change of GFR).

Results Mean age of the study population was 58.2 years, and the mean GFR was 44.9 ml/min per 1.73 m²; 48% of patients had diabetes. None of the lipid or lipoprotein measures was independently associated with risk of the composite end point or rate of change in GFR. However, there were significant ($P=0.01$) interactions by level of proteinuria. In participants with proteinuria <0.2 g/d, 1-SD higher LDL-C was associated with a 26% lower risk of the renal end point (hazard ratio [HR], 0.74; 95% confidence interval [95% CI], 0.59 to 0.92; $P=0.01$), and 1-SD higher total cholesterol was associated with a 23% lower risk of the renal end point (HR, 0.77; 95% CI, 0.62 to 0.96; $P=0.02$). In participants with proteinuria >0.2 g/d, neither LDL-C (HR, 0.98; 95% CI, 0.98 to 1.05) nor total cholesterol levels were associated with renal outcomes. Treatment with statins was reported in 55% of patients and was differential across lipid categories.

Conclusions In this large cohort of patients with CKD, total cholesterol, triglycerides, VLDL-C, LDL-C, HDL-C, apoA-I, apoB, and Lp(a) were not independently associated with progression of kidney disease. There was an inverse relationship between LDL-C and total cholesterol levels and kidney disease outcomes in patients with low levels of proteinuria.

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Introduction

Dyslipidemia is common among patients with CKD (1) and is characterized by elevated plasma triglycerides and VLDL cholesterol (VLDL-C) and reduced HDL cholesterol (HDL-C) concentrations (2). Animal studies have shown development and progression of kidney damage in the setting of hyperlipidemia with increased glomerulosclerosis and tubulointerstitial damage (3–6). In epidemiologic studies, the presence of dyslipidemia was associated with a higher risk of development of incident CKD in the general population (7–9). The association between dyslipidemia and progression of established kidney disease is not consistent in studies of diabetic (10) and nondiabetic (11–15) participants. These inconsistent findings may have resulted from the relatively small number of patients, low event rates, and concurrent lipid-lowering therapy. In addition, analyses of data from large, interventional studies on the effects of lipid-lowering agents have not shown a consistent benefit on progression of kidney disease

(16,17). Therefore, the role of dyslipidemia as a predictor or mediator of decline in renal function in patients with CKD is unclear.

The objective of this study was to evaluate whether measures of plasma lipids and lipoproteins predict progression of kidney disease, as defined by rate of change in eGFR, significant declines in eGFR, and development of ESRD in a multicenter cohort of patients with CKD. We hypothesized that baseline lipid and lipoprotein measures are independently associated with kidney disease outcomes.

Materials and Methods

The design, methods, and baseline characteristics of the Chronic Renal Insufficiency Cohort (CRIC) study population have been published (18,19). Briefly, CRIC is a prospective observational study of patients with mild-to-moderate kidney disease that was established by the National Institute of Diabetes and Digestive

*Department of Medicine, Case Western Reserve University, University Hospitals Case Medical Center, Louis Stokes Cleveland Veterans Affairs Medical Center, Cleveland, Ohio; [†]Center for Clinical Epidemiology and Biostatistics and ^{**}Division of Translational Medicine and Human Genetics, University of Pennsylvania, Philadelphia, Pennsylvania; [‡]Division of Nephrology, University of Illinois, Chicago, Illinois; [§]Department of Epidemiology, Tulane University, New Orleans, Louisiana; ^{||}Welch Center for Prevention, Epidemiology and Clinical Research, Johns Hopkins University, Baltimore, Maryland; [¶]Division of Nephrology, George Washington University, Washington, DC; ^{**}Case Western Reserve University, MetroHealth Medical Center, Cleveland, Ohio; and ^{††}University Hospitals Case Medical Center, Cleveland, Ohio

Correspondence:

Dr. Mahboob Rahman, 11100 Euclid Avenue, Cleveland, OH 44106. Email: Mahboob.Rahman@uhhospitals.org

and Kidney Diseases to examine risk factors for kidney and cardiovascular disease progression in CKD. A total of 3939 participants aged 21–74 years were enrolled from seven clinical centers throughout the United States (Ann Arbor, MI; Baltimore, MD; Chicago, IL; Cleveland, OH; New Orleans, LA; Philadelphia, PA; and Oakland, CA) between June 2003 and September 2008. The CRIC protocol was approved by the local institutional review board at each of the clinical centers, and all participants provided written informed consent. CRIC participants have been followed and seen annually for study visits until death or withdrawal of informed consent.

Inclusion in the CRIC study was based on age-specific eGFRs as follows: eGFR of 20–70 ml/min per 1.73 m² for patients age 21–44 years, 20–60 ml/min per 1.73 m² for patients age 45–64 years, and 20–50 ml/min per 1.73 m² for patients age 65–74 years. Major exclusion criteria were polycystic kidney disease, additional primary renal diseases requiring active immunosuppression, and significant coexisting illnesses likely to affect survival as previously published (18). All participants completed a baseline visit, during which sociodemographic characteristics, medical history, lifestyle behaviors, current medications, and anthropomorphic measurements were recorded. BP measurements were obtained using a standardized protocol and calibrated sphygmomanometers. In addition, plasma and urine samples were collected for measurement of study variables. History of cardiovascular disease (congestive heart failure, myocardial infarction/prior revascularization, peripheral vascular disease) was collected from the medical history questionnaire completed at the baseline visit.

Hypertension was defined as systolic BP \geq 140 mmHg, diastolic BP \geq 90 mmHg, or self-reported use of antihypertensive medications. Diabetes was defined as a fasting glucose \geq 126 mg/dl, random glucose \geq 200 mg/dl, or use of insulin or other antidiabetic medication. Serum creatinine was measured at the University of Pennsylvania laboratory and standardized to isotope-dilution mass spectrometry reference values (20). The eGFR was calculated using the CRIC equation (21). Plasma lipids and lipoproteins were measured using standard laboratory assays; triglycerides, total cholesterol, and HDL-C were measured by spectrophotometry; VLDL-C and LDL-C were directly measured after separation by ultracentrifugation (β quantification), and apoA-I, apoB, and lipoprotein(a) [Lp(a)] were measured using immunoturbidimetric assays. The blood sample was obtained in a fasting state in 96% of patients. The malnutrition/inflammation complex was defined by body mass index $<$ 23 kg/m², C-reactive protein \geq 10 mg/L, albumin $<$ 3.6 g/dl, or IL-6 $>$ 3.09 pg/ml (22).

The kidney disease outcomes evaluated in this paper are rate of eGFR decline per year and incidence of 50% decline in eGFR from baseline or development ESRD. Serum creatinine measurements to calculate slope of eGFR over time were obtained at annual visits.

Statistical Analyses

Demographic information and other baseline variables were described using mean \pm SD or median and interquartile range, when appropriate, for continuous variables and frequency and proportion for categorical variables. The lipid variable distributions across baseline eGFR categories were

compared using ANOVA for total cholesterol, LDL-C, HDL-C, apoA-I, and apoB and Wilcoxon rank-sum test for VLDL-C, triglycerides, and Lp(a). Because of their skewed distributions, VLDL-C, triglycerides, and Lp(a) were log transformed in all subsequent analyses.

To identify risk factors for progression of kidney disease, we conducted two sets of analyses: failure time analysis and repeated eGFR analysis. In failure time analysis, Cox proportional hazards models were fit using a composite renal end point of ESRD or 50% decline in eGFR from baseline as the primary end point (23). Patients were censored at the end of the follow-up time period (March 31, 2011), loss to follow-up, or death. We started with the unadjusted analysis showing the association between each of the lipoprotein variables and outcome in terms of hazards ratios (HRs) per 1-SD increase of the variable, followed by the multivariable models adjusting for the following baseline covariates: age, race/ethnicity, sex, systolic and diastolic BP, statin use, diabetes, smoking, 24-hour urine total protein excretion, body mass index, alcohol use, baseline eGFR, and clinical site. Stratified analyses were performed in subgroups defined by baseline diabetic status, statin use, malnutrition/inflammation complex, eGFR, and 24-hour urine total protein excretion level. Formal tests of interaction for each lipoprotein predictor were done by including the two-way interaction terms between the lipoprotein variable and all other covariates in the model. In the analyses of repeated eGFR measures, we estimated the associations between each lipoprotein measure with the slope of eGFR decline over the follow-up period using linear mixed effects models with both random intercept and slope terms (24). Parameter estimates were reported as the slope difference per 1-SD increase of the lipoprotein variable. In the multivariable adjusted model, we adjusted for the same covariates as were in the survival analysis (SAS 9.3; SAS Institute, Cary, NC).

Results

Baseline characteristics of the study population are described in Table 1. The mean age of the study population was 58.2 years; 55% of patients were male and 42% were non-Hispanic black. Most patients (86%) had a history of hypertension, and slightly less than half (48%) were diabetic. Treatment with statins was reported in 55% of patients; in addition, 13% of patients reported use of lipid-lowering therapy other than statins. There were several differences in baseline characteristics between patients in the low and high total cholesterol strata. Patients with low total cholesterol were older; were more likely to be men, be white, and have hypertension, diabetes, or prior cardiovascular disease; to be receiving statins and have a lower GFR and BP; and to be receiving an angiotensin-converting enzyme inhibitor.

At baseline, in cross-sectional analyses, low eGFR was associated with lower LDL-C, HDL-C, and Apo A1 and higher VLDL-C and triglycerides and Lp(a) (Table 2).

During the median follow-up of 4.1 years, 752 patients (4.7 per 100 patient years) reached ESRD, and 986 patients (6.1 per 100 patient-years) reached the combined end point of ESRD or 50% decline in GFR. The mean rate of change of GFR for the study population was -1.5 ml/min per 1.73 m²/per year. Figure 1 shows the crude event rates for the combined end point of ESRD or 50% decline in eGFR by quartiles of total cholesterol.

Table 1. Clinical and demographic characteristics of the Chronic Renal Insufficiency Cohort study population stratified by quartiles of baseline total cholesterol

Characteristic	All (n=3939)	Quartiles of Total Cholesterol at Baseline				P Value for Trend
		≤152 mg/dl (n=1003)	>152 to ≤178 mg/dl (n=972)	>178 to ≤209 mg/dl (n=993)	>209 mg/dl (n=958)	
Age (yr)	58.2±11.0	59.4±10.7	59.0±10.6	57.9±11.1	56.3±11.4	<0.001
Women, n (%)	1778 (45.1)	331 (33.0)	424 (43.6)	476 (47.9)	540 (56.4)	<0.001
Race/ethnicity, n (%)						
Non-Hispanic black	1650 (41.9)	378 (37.7)	415 (42.7)	423 (42.6)	425 (44.4)	0.02
Non-Hispanic white	1638 (41.6)	453 (45.2)	410 (42.2)	415 (41.8)	358 (37.4)	
Hispanic	497 (12.6)	125 (12.5)	113 (11.6)	118 (11.9)	139 (14.5)	
Other	154 (3.91)	47 (4.7)	34 (3.5)	37 (3.7)	36 (3.8)	
Hypertension, n (%)	3391 (86.1)	885 (88.2)	855 (88)	834 (84)	806 (84.1)	0.001
Diabetes, n (%)	1908 (48.4)	601 (59.9)	500 (51.4)	409 (41.2)	394 (41.1)	<0.001
History of myocardial infarction/ prior revascularization, n (%)	862 (21.9)	332 (33.1)	228 (23.5)	162 (16.3)	137 (14.3)	<0.001
History of congestive heart failure, n (%)	382 (9.70)	134 (13.4)	106 (10.9)	70 (7)	68 (7.1)	<0.001
History of peripheral vascular disease, n (%)	262 (6.65)	85 (8.5)	67 (6.9)	61 (6.1)	47 (4.9)	0.001
Current smoker, n (%)	517 (13.1)	136 (13.6)	114 (11.7)	128 (12.9)	135 (14.1)	0.58
Systolic BP (mmHg)	128.5±22.2	127.0±21.62	127.2±21.03	128.5±22.05	131.5±23.79	<0.001
Diastolic BP (mmHg)	71.5±12.8	69.2±12.55	69.5±12.40	72.7±12.83	74.9±12.62	<0.001
Body mass index (kg/m ²)	32.1±7.8	32.2±7.61	32.9±8.52	31.6±7.41	31.7±7.63	0.02
ACE inhibitor or ARB, n (%)	2689 (68.8)	736 (73.7)	714 (74)	640 (64.8)	592 (62.6)	<0.001
Statins, n (%)	2153 (55.0)	742 (74.3)	612 (63.4)	479 (48.5)	314 (33.2)	<0.001
Lipid-lowering medications other than statins, n (%)	527 (13.5)	188 (18.8)	130 (13.5)	98 (9.9)	109 (11.5)	<0.001
eGFR (ml/min per 1.73 m ²)	44.9 (16.8)	43.4 (16.06)	44.3 (17.02)	46.8 (17.11)	45.2 (17.04)	0.001
Serum creatinine (mg/dl)	1.7 (0.6)	1.79 (0.54)	1.76 (0.61)	1.69 (0.57)	1.73 (0.59)	0.001
24-hr urine protein (g/24 hr)	0.18 (0.07-0.91)	0.20 (0.08-0.75)	0.17 (0.07-0.82)	0.14 (0.07-0.78)	0.23 (0.07-1.66)	0.001
Hemoglobin (g/dl)	12.6±1.8	12.4±1.84	12.5±1.73	12.8±1.76	12.8±1.74	<0.001
Hemoglobin A1c (%)	6.7±1.6	6.7±1.46	6.7±1.51	6.5±1.53	6.7±1.74	0.1
Glucose (mg/dl)	115.4±51.7	116.8±53.0	114.7±45.2	114.7±52.2	115.6±55.8	0.61
C-reactive protein (mg/L)	2.57 (1.05-6.51)	2.40 (0.96-6.24)	2.63 (1.08-6.42)	2.53 (1.02-6.47)	2.69 (1.16-6.77)	0.03
Serum albumin (g/dl)	3.9±0.5	3.89±0.43	3.95±0.42	3.96±0.47	3.94±0.57	0.01
IL-6 (pg/ml)	1.90 (1.17-3.15)	2.19 (1.31-3.82)	1.91 (1.19-3.22)	1.78 (1.09-2.95)	1.80 (1.08-2.83)	0.002
Malnutrition/inflammation (%) ^a	1819 (46.6)	493 (49.5)	427 (44.3)	449 (45.5)	437 (46.1)	0.2

Values expressed with a plus/minus sign are the mean ±SD. Values with ranges are the median (interquartile range). ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker.

^aAs defined by body mass index <23 kg/m², C-reactive protein ≥10 mg/L, albumin <3.6 g/dl, or IL-6 >3.09 pg/ml.

Table 2. Lipoproteins stratified by baseline eGFR in the Chronic Renal Insufficiency Cohort study

Lipoprotein	Overall (n=3939)	eGFR<30 ml/min per 1.73 m ² (n=806)	eGFR 30 to <40 ml/min per 1.73 m ² (n=902)	eGFR 40 to <50 ml/min per 1.73 m ² (n=859)	eGFR 50 to <60 ml/min per 1.73 m ² (n=668)	eGFR≥60 ml/min per 1.73 m ² (n=702)	P Value
Total cholesterol (mg/dl)	183.7±45.6	182.9±52.9	182.6±44.5	183.5±46.2	183.2±43.0	186.6±39.1	0.45
LDL cholesterol (mg/dl)	102.7±35.6	99.1±38.9	100.3±34.6	102.3±36.2	104.6±34.2	108.6±32.4	<0.001
HDL cholesterol (mg/dl)	47.5±15.5	45.2±14.6	47.0±15.5	47.2±14.9	47.9±15.4	50.8±16.7	<0.001
VLDL cholesterol (mg/dl)	27 (17–42)	31 (19–47)	30 (19–43)	29 (17–43)	25 (15–39)	22 (13–35)	<0.001
Triglycerides (mg/dl)	128.5 (89–186)	139 (100–205)	135 (94–196)	133 (92–193)	120 (84–177)	109 (79–156)	<0.001
Lp(a) (mg/dl)	24.5 (9–59)	31.3 (12–69)	26.45 (9–63)	23.35 (8–64)	23 (8–53)	18.3 (7–46)	<0.001
ApoA-I	136.7±29.6	132.4±28.7	136.7±30.9	136.2±29.3	137.1±28.6	141.6±29.4	<0.001
ApoB	84.2±24.6	85.1±28.0	83.8±24.0	83.9±24.6	83.9±23.5	84.5±22.3	0.82

Values expressed with a plus/minus sign are the mean±SD. Values expressed with ranges are the median (interquartile range). Lp(a), lipoprotein(a).

The associations of lipoproteins and the composite kidney end point (unadjusted and adjusted) are presented in Table 3. Although there was an association in unadjusted models, after adjustment for covariates, total cholesterol, LDL-C, HDL-C, triglycerides, apoA-I, apoB, and Lp(a) levels were not independently predictive of the renal end point. The possibility of a nonlinear relationship between total cholesterol and outcomes was explored by adding a higher-order term in the model; the adjusted HR remained similar (0.95; *P*=0.23). Additional adjustment for albumin, IL-6, and history of cardiovascular disease did not change the association between lipid variables and outcomes (Supplemental Table 1). Analyses accounting for death as a competing risk also did not change the association between lipid variable and outcomes (Supplemental Table 2).

Subgroup analyses examined the relationships of lipoprotein measures and renal outcomes stratified by proteinuria, diabetes, statin use, presence of malnutrition/inflammation, and eGFR. The association between LDL and renal outcomes was significantly different according to level of proteinuria (interaction *P*=0.01). In participants with low levels of proteinuria (<0.2 g total protein/d; *n*=1916), a 1-SD higher LDL-C was associated with a 26% lower risk of the composite renal end point (HR, 0.74; 95% confidence interval [95% CI], 0.59 to 0.92; *P*=0.01) (Figure 2). In participants with higher levels of proteinuria (>0.2 g total protein/d), there was no significant association (HR, 0.96; *P*=0.26). Similarly, the association between total cholesterol and renal outcomes differed according to level of proteinuria (*P* for interaction =0.01) (Figure 3). One SD higher total cholesterol was associated with a 23% lower risk of the composite renal end point (HR, 0.77; 95% CI, 0.62 to 0.96; *P*=0.02) in participants with proteinuria<0.2 g/d, whereas there was no significant association between total cholesterol and outcomes in patients with proteinuria>0.2 g/d. The associations between all lipoproteins and renal outcomes were consistent across subgroups of diabetes, statin use, presence of malnutrition/inflammation, and eGFR (Figures 2 and 3, Supplemental Figures 1–6).

To explore the unexpected association between high LDL-C and lower risk of renal outcomes in patients with lower levels of proteinuria, we stratified baseline characteristics by level of proteinuria (Supplemental Table 3). Baseline characteristics significantly differed between participants with low (<0.2 g/d) and those with high (>0.2 g/d) levels of proteinuria. Given the higher use of statins in the low proteinuria group, analyses were further stratified by the use of statins and level of proteinuria. In participants with proteinuria<0.2 g/d who were receiving statin therapy, higher LDL-C (HR, 0.59; 95% CI, 0.43 to 0.82) and total cholesterol (HR, 0.67; 95% CI, 0.49 to 0.92) were associated with lower risk of the composite renal outcome. This association was attenuated and not statistically significant in participants with proteinuria<0.2 g/d who were not receiving statin therapy (HR, 0.89 and 0.87 for LDL-C and total cholesterol, respectively; *P*>0.05). Finally, within the subgroup of patients with lower levels of proteinuria, there were several differences in baseline characteristics upon stratification by baseline total cholesterol (Supplemental Table 4).

The association between baseline lipoproteins and rate of change of GFR over time is presented in Table 4. Although

several lipoproteins were predictive of rate of change of GFR in unadjusted analyses, none of the measures was independently predictive after adjustment for other factors that may influence rate of change of GFR. This was consistent when variables were stratified by proteinuria level at baseline (Table 5). Three-way interactions between statin use, proteinuria, and LDL ($P=0.61$) and total cholesterol ($P=0.71$) were not statistically significant.

Discussion

In this large cohort of patients with CKD, total cholesterol, triglycerides, VLDL-C, LDL-C, HDL-C, apoA-I, and apoB were not independently associated with progression of kidney disease. There was a borderline association between high Lp(a) levels and renal outcomes. However, there was a

significant interaction by proteinuria. In patients with proteinuria <0.2 g/d, higher LDL-C and total cholesterol levels were associated with lower risk of kidney disease outcomes, whereas there was no significant association of LDL-C or total cholesterol levels and kidney disease outcomes in patients with proteinuria >0.2 g/d.

Dyslipidemia is common in patients with CKD and is characterized by elevated plasma triglyceride and VLDL-C levels and diminished plasma HDL-C concentrations (25). This pattern in the lipid profile was also seen at baseline in CRIC study participants (26). The association of LDL-C and its major protein apoB with kidney outcomes has been inconsistent in previous studies. In studies of patients with CKD (12) and without CKD (8), LDL-C and ApoB were significantly associated with a more rapid decline in renal function. Our study found no statistically significant association between LDL-C or apoB and CKD progression in the overall CRIC population, consistent with the Modification of Diet in Renal Disease and Atherosclerosis Research in Communities (ARIC) studies, as well as the Study of Heart and Renal Protection (SHARP) clinical trial, where statin/ezetimibe therapy was not associated with reduction in progression of kidney disease (9,11,27,28). However, total and LDL-C cholesterol levels were inversely associated with progression of kidney disease in patients with low levels of proteinuria, particularly those receiving statin therapy. The factors underlying this seemingly paradoxical relationship are unclear; participants in the lower cholesterol quartiles had more risk factors for progression and were more likely to be taking statins, perhaps reflecting a higher vascular risk. Although the relationship remained strong after adjustment for relevant covariates in multivariate analyses, it is possible that some residual confounding may contribute to this finding. In addition, there may be unmeasured factors contributing to confounding that cannot be accounted for in the analyses. This is supported by the significant differences in risk factor profile within the low proteinuria subgroup when stratified by baseline cholesterol, as noted in Supplemental

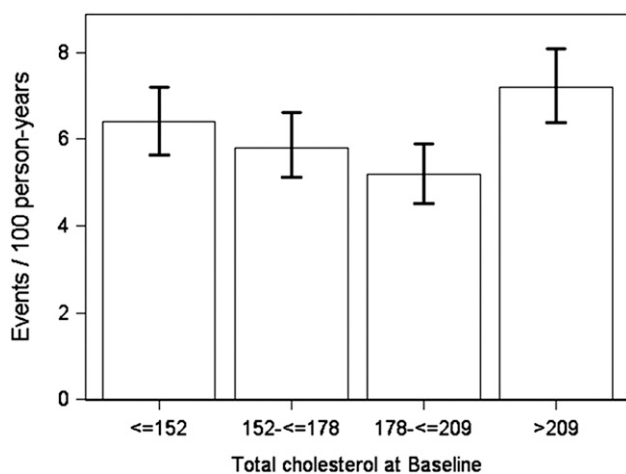


Figure 1. | Crude event rates for ESRD or 50% decline in GFR stratified by quartiles of total cholesterol (mg/dl) at baseline. The error bars delineate the 95% confidence interval.

Table 3. Associations between baseline lipoproteins and the composite end point of ESRD or 50% decline in GFR in the Chronic Renal Insufficiency Cohort study

Lipoprotein	Unadjusted		Adjusted ^a	
	Hazard Ratio ^b (95% CI)	P Value	Hazard Ratio ^b (95% CI)	P Value
Total cholesterol	1.15 (1.08 to 1.23)	<0.01	1.00 (0.93 to 1.07)	0.98
LDL cholesterol	1.01 (0.95 to 1.08)	0.68	0.95 (0.89 to 1.02)	0.14
HDL cholesterol	0.87 (0.81 to 0.93)	<0.01	1.00 (0.92 to 1.08)	0.95
VLDL cholesterol ^c	1.33 (1.25 to 1.42)	<0.01	1.06 (0.99 to 1.14)	0.11
Triglycerides ^c	1.26 (1.19 to 1.34)	<0.01	1.05 (0.97 to 1.12)	0.21
Lp(a) ^c	1.26 (1.18 to 1.35)	<0.01	1.07 (0.99 to 1.15)	0.09
ApoA-I	0.93 (0.87 to 1.00)	0.04	1.01 (0.93 to 1.10)	0.75
ApoB	1.23 (1.15 to 1.30)	<0.01	1.00 (0.94 to 1.07)	0.95

Lp(a), lipoprotein(a).

^aModel adjusted for age, race, sex, diabetes, BP, statin use at baseline, smoking, 24-hour urine protein excretion, body mass index, clinical center, alcohol use, and baseline eGFR.

^bHazard ratios reported as per 1-SD change in independent variable.

^cValues were log transformed.

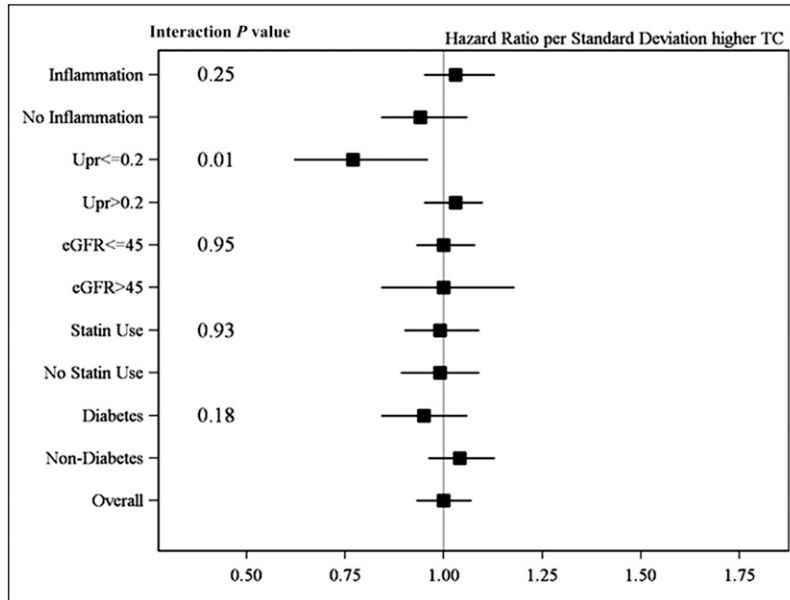


Figure 2. | Hazards ratios for renal outcome (ESRD or 50% decline in GFR) per 1-SD increase in total cholesterol (TC) in subgroups of inflammation/malnutrition, proteinuria, eGFR, statin use, and diabetes. Model adjusted for age, race, sex, diabetes, BP, statin use at baseline, smoking, 24-hour urine protein (UPr) excretion, body mass index, clinical center, alcohol use, and baseline eGFR. The error bars delineate the 95% confidence interval.

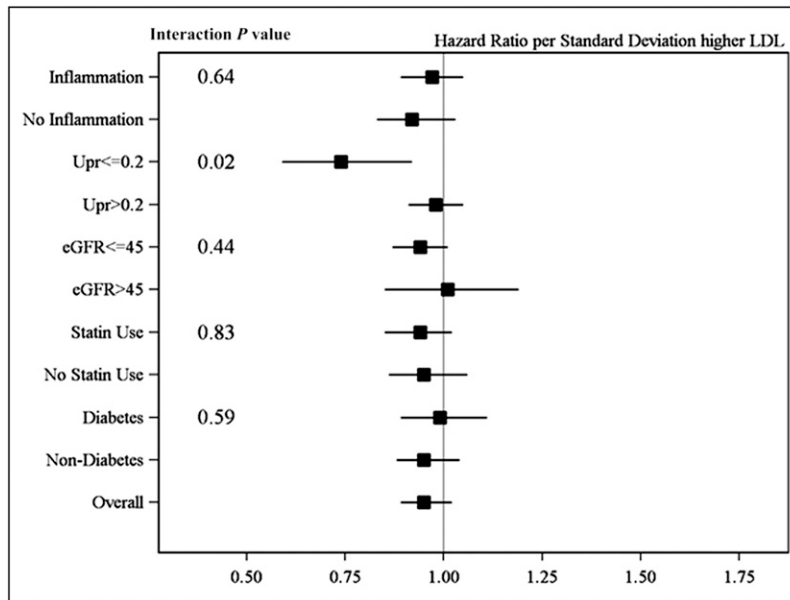


Figure 3. | Hazard ratios for renal outcome (ESRD or 50% decline in GFR) per 1-SD increase in LDL cholesterol in subgroups of inflammation/malnutrition, proteinuria, eGFR, statin use, and diabetes. Model adjusted for age, race, sex, diabetes, BP, statin use at baseline, smoking, 24-hour urine protein (UPr) excretion, body mass index, clinical center, alcohol use, baseline eGFR. The error bars delineate the 95% confidence interval.

Table 4. Another possibility is that because proteinuria is such a robust risk factor for progression of kidney disease, it may overwhelm the effect of other risk factors. In addition, as seen in Supplemental Table 3, patients with higher levels of proteinuria are more likely to have other risk factors for progression of CKD. In the absence of significant proteinuria, the relationship between LDL-C and outcomes may be

easier to detect. Lastly, we evaluated the presence of malnutrition/inflammation as a confounder; in the setting of ESRD, a seemingly paradoxical relationship is seen between cholesterol levels and mortality. However, in the absence of malnutrition/inflammation, high cholesterol levels are associated with higher rates of mortality (22). In our study, results were consistent when stratified by malnutrition/

Table 4. Associations between baseline lipoproteins and the rate of GFR decline in the Chronic Renal Insufficiency Cohort study

Lipoprotein	Unadjusted		Adjusted ^a	
	Slope Difference ^b per 1 SD Higher of Lipoprotein Variable (95% CI)	P Value	Slope Difference ^b per 1 SD Higher of Lipoprotein Variable (95% CI)	P Value
Total cholesterol	-0.20 (-0.32 to -0.08)	<0.01	-0.00 (-0.12 to 0.11)	0.94
LDL cholesterol	-0.07 (-0.18 to 0.05)	0.26	0.03 (-0.08 to 0.14)	0.56
HDL cholesterol	0.10 (-0.01 to 0.21)	0.06	-0.03 (-0.14 to 0.08)	0.57
VLDL cholesterol ^c	-0.25 (-0.36 to -0.14)	<0.01	0.01 (-0.09 to 0.11)	0.80
Triglycerides ^c	-0.21 (-0.32 to -0.09)	<0.01	0.05 (-0.06 to 0.15)	0.39
Lp(a) ^c	-0.19 (-0.30 to -0.08)	<0.01	0.01 (-0.10 to 0.12)	0.84
ApoA-I	0.05 (-0.06 to 0.16)	0.37	0.03 (-0.09 to 0.14)	0.66
ApoB	-0.23 (-0.35 to -0.11)	<0.01	0.06 (-0.05 to 0.17)	0.30

Lp(a), lipoprotein(a).
^aModel adjusted for age, race, sex, diabetes, BP, statin use at baseline, smoking, 24-hour urine protein excretion, body mass index, clinical center, alcohol use, and baseline eGFR per 1-SD change in independent variable.
^bSlope difference in ml/min per 1.73 m² per year; a negative slope difference indicates a faster decline in GFR.
^cValues were log transformed.

Table 5. Associations between baseline lipoprotein measures and the rate of eGFR decline stratified by proteinuria at baseline in the Chronic Renal Insufficiency Cohort study

Lipoprotein	24-hr Urinary Protein ≤0.2 g/d		24-hr Urinary Protein >0.2 g/d	
	Slope Difference ^b per 1 SD Higher of Lipoprotein Variable (95% CI)	P Value	Slope Difference ^b per 1 SD Higher of Lipoprotein Variable (95% CI)	P Value
Total cholesterol	0.10 (-0.05 to 0.25)	0.19	-0.12 (-0.29 to 0.06)	0.19
LDL cholesterol	0.11 (-0.04 to 0.25)	0.15	-0.03 (-0.20 to 0.13)	0.68
HDL cholesterol	-0.01 (-0.14 to 0.12)	0.86	-0.05 (-0.24 to 0.14)	0.59
VLDL cholesterol ^b	0.06 (-0.06 to 0.19)	0.34	-0.06 (-0.23 to 0.10)	0.46
Triglycerides ^b	0.09 (-0.04 to 0.22)	0.19	-0.02 (-0.18 to 0.15)	0.84
Lp(a) ^b	0.04 (-0.09 to 0.17)	0.52	-0.03 (-0.21 to 0.15)	0.73
ApoA-I	0.07 (-0.06 to 0.21)	0.29	-0.04 (-0.23 to 0.15)	0.70
ApoB	0.15 (0.01 to 0.29)	0.03	-0.04 (-0.22 to 0.13)	0.61

Lp(a), lipoprotein(a).
^aModel adjusted for age, race, sex, diabetes, BP, statin use at baseline, smoking, 24-hour urine protein excretion, body mass index, clinical center, alcohol use, and baseline eGFR per 1-SD change in independent variable. Slope difference in ml/min per 1.73 m² per year; a negative slope difference indicates a faster decline in GFR.
^bValues were log transformed.

inflammation, suggesting that the relationship between LDL-C cholesterol and progression of CKD is not confounded by the presence of malnutrition/inflammation. Of note, there was no relationship between total and LDL cholesterol levels and rate of change in GFR in the low proteinuria group (Table 5). This may relate to the overall slow decline in GFR in patients with lower levels of proteinuria with less power to detect an association; in addition, as shown in the African American Study of Kidney Disease and Hypertension study, nonlinear, abrupt declines in GFR are not uncommon in individual patients (29). This may contribute to why an association was seen between LDL and total cholesterol and clinical renal outcomes, but not with rate of decline in GFR.

Studies of the relationship between triglyceride levels and CKD progression have also been inconsistent. In the ARIC study, high triglycerides were associated with a rise in serum creatinine (9). Similarly, in a cohort of patients with IgA nephropathy, hypertriglyceridemia was independently associated with a 20% increase in serum creatinine levels above baseline (30). However, other studies have failed to show an association between triglycerides and progression of CKD (11,12). Our results, in the largest prospective study to date, demonstrate that VLDL-C and triglycerides are not independently predictive of progression of kidney disease.

Previous longitudinal studies evaluating HDL-C and apoA-I levels as predictors of decline in kidney function

have been inconsistent; some studies have shown that low HDL-C and apoA-I levels were associated with a faster rate of progression of kidney disease (7–9,29), while others have not (12). In our study, neither HDL-C nor apoA-I levels were associated with kidney disease outcomes.

Although Lp(a) is a predictor of atherosclerotic cardiovascular disease in the general population, whether it predicts progression of kidney disease is not known (31). Lp(a) levels are known to increase early during the course of CKD and become more pronounced with increased severity of the disease (32,33), although some studies show a stronger association of Lp(a) with proteinuria than with GFR (34). In a prospective study in patients with type 2 diabetes who have overt proteinuria, an elevated Lp(a) level was an independent risk factor for the progression of diabetic nephropathy (35). In our study, Lp(a) levels were higher in patients with lower GFR and strongly predicted renal outcomes in unadjusted analyses. However, after adjustment for other known risk factors for progression, the association of Lp(a), even among the subpopulation with diabetes, was markedly attenuated and was not statistically significant. This suggests that effects of Lp(a) seen in previous studies may be confounded by other coexistent risk factors, but does not rule out a smaller association between Lp(a) levels and outcomes of kidney disease progression.

Our study makes an important contribution to the literature; as the largest study of the association between dyslipidemia and kidney disease progression in patients with CKD, it demonstrated that the lipids and lipoproteins measured in these analyses do not independently predict progression of kidney disease in the setting of CKD. Because they were obtained from an epidemiologic study, these data cannot directly address mechanisms of disease progression. Therefore, they do not rule out the role of dyslipidemia in progression of kidney disease; however, they do suggest that these effects may be mediated through other pathways and highlight the need for novel markers of lipid metabolism in the patients with CKD.

Our study has several strengths. The large sample size and availability of detailed, high-quality information on comorbidity and other risk factors in the CRIC study allowed for robust multivariate analyses to ascertain independent associations between lipoprotein measures and outcomes. In addition, the large proportion of minority and diabetic patients helps overcome the shortcomings of previous studies and enhances the generalizability of the findings. Our study also has important limitations. Most patients were receiving statins or other lipid-lowering therapy, which typically decreases total cholesterol, LDL-C, and, to a lesser extent, triglycerides. Statin use was more common in patients in the lowest quartile than the higher quartiles of cholesterol. Despite this limitation, the stratified analyses by baseline statin use were consistent with overall results. This study did not evaluate novel measures of lipoproteins measured by nuclear magnetic resonance spectroscopy (such as plasma apoC-III) that have been associated in cross-sectional studies with kidney function (37). The current analysis also did not assess whether dyslipidemia contributes to the high risk of cardiovascular disease seen in CKD, but future reports from the CRIC study will do so. Finally, it is possible that some of the seemingly paradoxical findings may simply relate to chance given the multiple comparisons performed in the analyses.

In summary, in this large cohort of patients with CKD, we report that total cholesterol, triglycerides, Lp(a), VLDL-C, LDL-C, HDL, apoA-I, and apoB were not independently associated with progression of kidney disease. We report an inverse relationship between LDL-C and total cholesterol levels and kidney disease outcomes in patients with low levels of proteinuria. Further research is needed to replicate these findings in other cohorts and to evaluate the pathophysiologic basis and implications of this seemingly paradoxical association.

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Disclosures

None.

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