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Serum Low-Density Lipoprotein Cholesterol and Cardiovascular Disease Risk Across Chronic Kidney Disease Stages (Data from 1.9 Million United States Veterans)

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In the general population, elevated low-density lipoprotein (LDL) cholesterol levels are an important risk factor for cardiovascular disease (CVD) and mortality; however, the association of LDL with mortality risk and cardiovascular events are less clear in chronic kidney disease (CKD). We sought to examine the relationship of LDL with mortality and rates of atherosclerotic cardiovascular disease (ASCVD) and non-atherosclerotic cardiovascular-related (non-ASCVD) hospitalizations across CKD stages. Our analytical cohort consisted of 1,972,851 United States veterans with serum LDL data between 2004 and 2006. Associations of LDL with all-cause and cardiovascular mortality across CKD stages were evaluated using Cox proportional hazard models with adjustment for demographics, comorbid conditions, smoking status, prescription of statins and non-statin lipid-lowering drugs, body mass index, albumin, high-density lipoprotein, and triglycerides. Associations between LDL and ASCVD and non-ASCVD hospitalizations were estimated using negative binomial regression models across CKD stages. The cohort consisted of 5% female, 14% Black, 29% diabetic, 33% statin-users, and 44% current smokers, with a mean patient age of 64 ± 14 years. Patients with high LDL (≥160 mg/dL) had a higher risk of all-cause and cardiovascular mortality as well as ASCVD and non-ASCVD hospitalization rates across all CKD stages compared with the reference (LDL 70 to <100 mg/dL). The associations with all-cause and cardiovascular mortality and ASCVD hospitalization rate were attenuated at higher CKD stages. These trends were reversed with amplification of the association of high LDL with non-ASCVD hospitalization at higher CKD stages. In conclusion, associations of LDL with mortality and both ASCVD and non-ASCVD hospitalizations are modified according to kidney disease stage. Published by Elsevier Inc. (Am J Cardiol 2022;170:47−55)

The prevalence of cardiovascular disease (CVD) in adults in the United States is 48%, increases with advancing age, and is the leading cause of death globally.[1] Thus, predicting and reducing CVD risk has been a top priority for clinical practice and public health. Low-density lipoprotein-cholesterol (LDL) is one of the most extensively studied exposure risks for atherosclerotic cardiovascular events (ASCVD) with evidence regarding its causal relation with

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atherosclerotic plaques.[2] Currently, 1 in 7 adults are affected by chronic kidney disease (CKD).[3]CKD has been reported as a risk factor for ASCVD.[4–6] Unfortunately, traditional cardiovascular (CV) risk factors fall short in estimating the risk of CVD events for patients with CKD.[7,8] Reduction in LDL with statins in patients with CKD can decrease the risk of ASCVD events similarly to the general population, but with attenuation of effectiveness with the progression of CKD.[4] This study aims to investigate the association of LDL with mortality and CVD events separating ASCVD events known to be reduced by statin intervention from non-ASCVD cardiovascular (non-ASCVD) events.

Methods

We conducted a retrospective study from the Lipid Profiles and Management in Veterans with CKD (LIPROVET) study, which is composed of all United States veterans who had at least 1 serum lipid (high-density lipoprotein cholesterol [HDL], LDL, total cholesterol [TC], or triglycerides [TG]) measurement from October 1, 2004, to September 30, 2006. Our source population consisted of 3,958,837 patients from the United States Veterans Affairs (VA) databases. In this study, we excluded patients without data on HDL, TC, and/or TG measurement (n = 114,031). We then excluded patients with calculated LDL<1 or >500 mg/dL (n = 192,469), patients missing an estimated glomerular filtration rate (eGFR) measured within 90 days before lipid measurement (n = 1,679,443), and patients with missing censoring information (n = 43). Our final cohort consisted of 1,972,851 veteran patients with a calculated serum LDL (Supplementary Figure 1).

All baseline patient demographic characteristics, laboratory measurements, comorbid conditions, social history including marital and smoking status, and medications of this study cohort have been previously described. Briefly, data were extracted from a combination of VA,[9] Centers for Medicare, Medicaid Services (CMS), and United States Renal Data System (USRDS) databases.[10,11] LDL was calculated by using the Martin-Hopkin's LDL calculation equation (LDL = TC−HDL−TG/novel factor)[12] from other lipid measurements taken on the same day. eGFR was calculated with the CKD Epidemiology Collaboration formula,[13] which was then used to categorize CKD stages of patients (non-CKD, 3A, 3B, 4, and 5) according to the KDIGO guidelines.[14] The USRDS records were used to identify end-stage renal disease (ESRD) patients who were on renal replacement therapy. Owing to a lower number of ESRD patients, they were grouped with CKD Stage 5, not on dialysis (eGFR<15 ml/min/1.73 m^2). The closest single measurement within 90 days of the index lipid measurement was used for all covariate laboratory measurements. VA/CMS pharmacy records were used to identify medications used at the time of the lipid measurement date.

The main exposure of this study was calculated LDL. Calculated LDL was categorized into 5 groups: (1) <70, (2) 70 to <100, (3) 100 to <130, (4) 130 to <160, and (5) ≥160 mg/dL, based on the distribution and clinically relevant thresholds.

The primary outcomes of interest were all-cause and cardiovascular mortality, hospitalizations for ASCVD events, and non-ASCVD events as defined in Supplementary Table 1. Follow-up began on the day of lipid measurement and ended at the time that subjects experienced death, ASCVD or non-ASCVD events, or censoring events. Patients were censored for the event of interest, death, lost to follow-up, or December 31, 2014, whichever occurred first. Mortality data, ASCVD and non-ASCVD records, censoring events, and lost to follow-up were extracted from VA, National Death Index, CMS, and USRDS data sources. Lost to follow-up was determined by the last date of active use of VA or CMS services (inpatient, outpatient, laboratory, or pharmacy). Cause of death was obtained solely from the National Death Index (by way of the VA Mortality Data Repository files), which was categorized by specific cardiovascular death International Classification Of Diseases, 10th Revision codes (Supplementary Table 1). Hospitalization data were obtained from VA/CMS databases. Records with the specific diagnostic code in the first or second position were considered as an event (Supplementary Table 1).

Patient baseline demographic and clinical characteristics were presented as mean ± SD, median (interquartile range [IQR]), or percentages as appropriate for the total cohort and stratified by serum LDL groups. Cox proportional hazard models were used to evaluate the association of LDL with all-cause, CV mortality and time-to-first ASCVD or non-ASCVD hospitalization. Negative binomial regression models were used to examine the relationship of LDL with hospitalization rate. Fine and Gray competing risk regression models were used to evaluate the association of LDL with ASCVD and non-ASCVD hospitalization. Competing events were all-cause mortality for both outcomes, non-ASCVD events where ASCVD events were the outcome of interest and vice versa where non-ASCVD events was the outcome of interest. All analyses were stratified by CKD stage. LDL of 70 to <100 mg/dL was used as the reference for each CKD stage.

For all analyses, 3 models of adjustment were used: (1) unadjusted; (2) case-mix adjusted, which included age, gender, race, ethnicity, the following comorbid conditions: smoking status, Charlson Comorbidity Index (CCI), myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, chronic pulmonary disease, dementia, liver disease, malignancy, diabetes mellitus, atrial fibrillation, hypertension, depression and ischemic heart disease; and use of statin therapy, and non-statin lipid-lowering drug therapy; and (3) fully adjusted, which included all covariates in the case-mix model plus baseline measures of body mass index (BMI), albumin, HDL, TG; systolic blood pressure (BP), diastolic BP, and medication use (angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, acetylsalicylic acid, beta-blockers, calcium channel blockers, diuretics, glucose-lowering medication, and clopidogrel). We considered the fully adjusted model as the primary model of interest.

In sensitivity analysis, we also examined the associations of continuous LDL with all-cause mortality, CV mortality, time to first ASCVD, and non-ASCVD hospitalization in the fully adjusted model using restricted cubic splines with 4 knots at the fifth, 35th, 65th, and 95th percentiles of LDL

for each CKD stage. We additionally examined associations of LDL with all-cause and CV mortality stratified by statin use at baseline, age< or ≥65 years, presence of cancer comorbidity, and baseline CCI< or ≥4). Missing categorical data on patient demographic characteristics, including race and ethnicity, were <1.4% and for smoking status was 4%, and were imputed using a missing category. Less than 1% of the total cohort had missing comorbid data and were categorized as an absence of condition for each comorbidity. Baseline albumin and BMI were missing in 27% and 11% of the cohort, respectively, and were imputed using means. All analyses were conducted using SAS Enterprise Guide, version 7.1 (Cary, North Carolina), and STATA Statistical Software Version 14.2 (StataCorp, College Station, Texas).

Results

This 1,972,851 United States veteran cohort was aged 64 ± 14 years (mean ± SD) and included 5% female patients, and 14% Black patients (Table 1). Patients had an average serum LDL of 109.96 ± 34.59 mg/dL. The median (IQR) eGFR was 75 (60, 91) ml/min/1.73 m^2, and 1% of the cohort were CKD Stage 5 and ESRD at the time of lipid-measurements.

Patients with higher LDL were younger, female, Black, not married, and a current smoker, yet had a lower prevalence of comorbidities and lower CCI (Table 1). Moreover, patients with higher LDL were more likely to have higher eGFR, TG, and TC, higher systolic and diastolic BP and a slightly higher BMI, whereas they were less likely to be on lipid-lowering medication.

During a median (IQR) follow-up of 9.2 (6.5 to 9.9) years, 685,285 patients died with a crude mortality rate of 44.2 deaths (95% confidence interval [CI] 44.1 to 44.3) per 1,000 person-years. There was also a total of 232,953 CV deaths, with a crude CV mortality rate of 15.0 (95% CI 14.9 to 15.1) per 1,000 person-years. In the total cohort, a linear inverse association was observed between LDL and all-cause and cardiovascular mortality in the unadjusted model, where patients with higher LDL had a lower risk of all-cause mortality compared with the reference (Supplementary Table 2). In adjusted models, the association became U-shaped where both lower and higher LDL were associated with a higher risk of mortality. This U-shaped association persisted across all CKD stages in the fully adjusted models (Figure 1). All-cause mortality risk was amplified with CKD stage worsening in patients with low LDL (LDL <70 mg/dL) whereas this trend was reversed in patients with higher LDL (LDL ≥100 mg/dL).

Similar results were found in restricted cubic spline models except in CKD Stage 5 and ESRD, where patients with LDL ≥100 mg/dL had a trend toward lower to null CV death (Supplementary Figure 3). Associations of LDL with all-cause and cardiovascular mortality were similar across strata of age, cancer comorbidity, statin use, and CCI (Supplementary Tables 6 and 7). A total of 662,366 (34%) patients were hospitalized during the follow-up period with a median 0 (IQR: 0, 1) hospitalizations. There were 1,003,722 and 1,520,695 hospitalization events in 526,965 and 662,366 unique patients owing to ASCVD and non-ASCVD, respectively. There was a linear association between serum LDL and ASCVD hospitalization rate in the fully adjusted model (Supplementary Table 3). After stratification by CKD stages, this linear relation between LDL and ASCVD hospitalization rate persisted across all CKD stages (Figure 2). In patients with LDL ≥160 mg/dL, ASCVD hospitalization rate attenuated as CKD progressed.

A U-shaped association was observed between serum LDL and non-ASCVD hospitalization events in the primary model; low LDL (<70 mg/dL) and high LDL (≥160 mg/dL) levels were associated with a higher rate of hospitalizations (Supplementary Table 3). This U-shaped association persisted even after stratification for CKD stages (Figure 2). Non-ASCVD hospitalization rate amplified with worsening of CKD stages in patients with LDL<70 mg/dL. However, unlike the ASCVD hospitalization rate, the non-ASCVD hospitalization rate increased as CKD progressed (non-CKD to CKD Stage 4) but dropped drastically in CKD Stage 5 and ESRD in patients with LDL ≥160 mg/dL.

Serum LDL was linearly associated with risk of time to first ASCVD hospitalization in the fully adjusted model; patients with LDL≥160 mg/dL had a 35% higher hospitalization risk compared with patients with LDL 70 to <100 mg/dL (Supplementary Table 4). The linear relation between LDL, and time to first ASCVD hospitalization carried on across all CKD strata (Figure 3). However, the risk of time to first ASCVD hospitalization declined as CKD stage advanced (non-CKD to CKD Stage 4) and then increased in CKD Stage 5 and ESRD in patients with LDL ≥160 mg/dL. The association between high LDL (≥100 mg/dL) and time to first ASCVD hospitalization rate decreased with worsening of CKD stages (Supplementary Figure 4).

Time to first non-ASCVD hospitalization, similar to the hospitalization rate, had a U-shaped relation with serum LDL after full adjustment and stratification by CKD stage (Figure 3). In patients with LDL <70 mg/dL, risk of time to first non-ASCVD hospitalization got higher as CKD worsened (Supplementary Table 4). There was also a trend toward the amplified ASCVD hospitalization rate as CKD progressed (non-CKD to CKD Stage 3B) in patients with LDL ≥160 mg/dL. Restricted cubic spline models showed similar results (Supplementary Figure 5).

Similar results were seen in competing risk analyses, where there was a linear and a U-shaped relation between serum LDL and ASCVD and non-ASCVD hospitalization, respectively in the total cohort (Figure 4). However, after CKD stratification, a trend was shown that ASCVD hospitalization risk attenuated as CKD progressed in LDL <70 mg/dL after the primary model of adjustment (Supplementary Table 5).

Discussion

We observed a U-shaped association between baseline serum LDL level and both all-cause and CV mortality across all CKD stages in the fully adjusted model. A linear relation and a U-shaped relation were observed between serum LDL and ASCVD and non-ASCVD hospitalization rate, respectively. ASCVD hospitalization

Table 1
Baseline characteristics of 1,972,851 patients stratified by serum low density lipoprotein

Variable	Serum LDL (mg/dL)					
	Total	<70	70−<100	100−<130	130−<160	≥160
n	1,972,851	200,716	630,772	637,671	343,000	160,692
CKD stage						
Non-CKD	1,492,645 (76%)	131,837 (66%)	447,593 (71%)	494,987 (78%)	282,912 (82%)	135,316 (84%)
3A	299,989 (15%)	36,956 (18%)	112,999 (18%)	93,160 (15%)	40,146 (12%)	16,728 (10%)
3B	130,097 (7%)	20,469 (10%)	51,393 (8%)	37,275 (6%)	14,805 (4%)	6,155 (4%)
4	34,898 (2%)	7,013 (3%)	13,406 (2%)	8,957 (1%)	3,695 (1%)	1,827 (1%)
5/ESRD	15,222 (1%)	4,441 (2%)	5,381 (1%)	3,292 (1%)	1,442 (0%)	666 (0%)
eGFR (mL/min/1.73m^2)	75 (60,91)	70 (53,87)	73 (57,87)	76 (62,91)	80 (65,93)	81 (67,94)
Age (years)	64±14	67±13	66±13	63±14	60±13	58±13
Women	97,625 (5%)	5,945 (3%)	24,124 (4%)	33,154 (5%)	21,840 (6%)	12,562 (8%)
Marital status						
Single	165,913 (8%)	15,602 (8%)	47,362 (8%)	54,369 (9%)	32,179 (9%)	16,401 (10%)
Married	1,104,450 (56%)	112,441 (56%)	366,466 (58%)	358,409 (56%)	184,919 (54%)	82,215 (51%)
Divorced	467,235 (24%)	43,702 (22%)	131,444 (21%)	151,188 (24%)	92,570 (27%)	48,331 (30%)
Widowed	225,728 (12%)	28,297 (14%)	82,924 (13%)	70,525 (11%)	31,232 (9%)	12,750 (8%)
Race						
White	1,597,586 (82%)	163,297 (82%)	523,306 (84%)	517,629 (82%)	270,783 (80%)	122,571 (78%)
Black	276,125 (14%)	28,894 (15%)	79,261 (13%)	87,613 (14%)	52,249 (16%)	28,108 (18%)
Others	72,098 (4%)	6,903 (3%)	21,728 (3%)	23,310 (4%)	13,494 (4%)	6,663 (4%)
Ethnicity						
Hispanics	73,550 (4%)	7,360 (4%)	21,855 (3%)	23,969 (4%)	13,916 (4%)	6,450 (4%)
Charlson comorbidity index	1 (0,2)	2 (1,3)	1 (0,3)	1 (0,2)	0 (0,1)	0 (0,1)
Comorbid conditions						
Myocardial infarction	126,651 (6%)	25,591 (13%)	53,740 (9%)	31,056 (5%)	11,096 (3%)	5,168 (3%)
Congestive Heart Failure	200,672 (10%)	41,725 (21%)	81,875 (13%)	50,715 (8%)	18,712 (5%)	7,645 (5%)
Peripheral vascular disease	188,156 (10%)	32,198 (16%)	76,777 (12%)	51,188 (8%)	19,605 (6%)	8,388 (5%)
Cerebrovascular disease	170,302 (9%)	26,545 (13%)	68,461 (11%)	48,107 (8%)	18,844 (6%)	8,345 (5%)
Dementia	51,444 (3%)	7,960 (4%)	18,781 (3%)	15,411 (2%)	6,690 (2%)	2,602 (2%)
Chronic pulmonary disease	358,427 (18%)	49,838 (25%)	128,012 (20%)	109,603 (17%)	50,314 (15%)	20,660 (13%)
Rheumatologic disease	38,584 (2%)	4,939 (2%)	13,426 (2%)	12,233 (2%)	5,658 (2%)	2,328 (1%)
Peptic ulcer disease	42,460 (2%)	6,538 (3%)	15,159 (2%)	12,714 (2%)	5,731 (2%)	2,318 (1%)
Hemiplegia/paraplegia	22,602 (1%)	3,360 (2%)	7,963 (1%)	6,841 (1%)	3,072 (1%)	1,366 (1%)
Renal disease	122,601 (6%)	25,162 (13%)	46,820 (7%)	31,671 (5%)	13,057 (4%)	5,891 (4%)
AIDS/HIV	11,165 (1%)	1,545 (0.8%)	3,458 (0.6%)	3,522 (0.6%)	1,857 (0.5%)	783 (0.5%)
Liver disease	61,358 (3%)	12,114 (6%)	20,694 (3%)	16,988 (3%)	8,047 (2%)	3,515 (2%)
Diabetes mellitus	567,291 (29%)	88,377 (44%)	224,823 (36%)	161,368 (25%)	64,537 (19%)	28,186 (18%)
Cancer	234,725 (12%)	30,800 (15%)	85,215 (14%)	73,578 (12%)	32,436 (9%)	12,696 (8%)
Hypothyroid	133,801 (7%)	17,263 (9%)	47,969 (8%)	40,950 (6%)	19,053 (6%)	8,566 (5%)
Anemia	221,207 (11%)	42,898 (21%)	85,106 (14%)	59,957 (9%)	23,880 (7%)	9,366 (6%)
Asthma	83,946 (4%)	9,419 (5%)	27,736 (4%)	27,175 (4%)	13,833 (4%)	5,783 (4%)
Atrial fibrillation	131,688 (7%)	25,225 (13%)	54,709 (9%)	35,197 (6%)	12,241 (4%)	4,316 (3%)
Hip/pelvic fracture	9,577 (0.5%)	1,874 (0.9%)	3,608 (0.6%)	2,615 (0.4%)	1,073 (0.3%)	407 (0.3%)
Hyperlipidemia	1,053,688 (53%)	116,887 (58%)	373,959 (59%)	316,740 (50%)	161,575 (47%)	84,527 (53%)
Hypertension	1,292,517 (66%)	154,020 (77%)	460,354 (73%)	406,735 (64%)	189,943 (55%)	81,465 (51%)
Ischemic heart disease	538,659 (27%)	93,447 (47%)	232,767 (37%)	140,512 (22%)	49,591 (14%)	22,342 (14%)
Osteoporosis	4,103 (0.2%)	576 (0.3%)	1,475 (0.2%)	1,286 (0.2%)	537 (0.2%)	229 (0.1%)
Depression	345,469 (18%)	36,037 (18%)	103,917 (16%)	110,674 (17%)	62,781 (18%)	32,060 (20%)
Anxiety	235,065 (12%)	22,586 (11%)	69,155 (11%)	76,365 (12%)	44,390 (13%)	22,569 (14%)
Substance abuse	132,109 (7%)	17,749 (9%)	39,172 (6%)	40,145 (6%)	22,956 (7%)	12,087 (8%)
Post-traumatic stress disorder	137,782 (7%)	12,113 (6%)	38,492 (6%)	45,168 (7%)	27,477 (8%)	14,532 (9%)
Smoker						
Never	544,956 (29%)	52,370 (27%)	174,264 (29%)	179,750 (29%)	95,741 (29%)	42,831 (28%)
Current	828,806 (44%)	82,869 (43%)	249,944 (41%)	266,614 (44%)	152,267 (47%)	77,112 (50%)
Past	517,610 (27%)	57,947 (30%)	182,356 (30%)	164,820 (27%)	79,272 (24%)	33,215 (22%)
Laboratory measurements						
Albumin (g/dL)	4.06±0.44	3.90±0.53	4.02±0.43	4.08±0.41	4.12±0.40	4.15±0.43
Alkaline phosphatase (U/L)	74 (60,90)	75 (60,95)	73 (60,89)	73 (60,89)	74 (61,90)	76 (63,92)
Blood urea nitrogen (mg/dL)	17.74±8.79	20.42±12.22	18.62±9.18	17.24±7.85	16.30±7.22	15.85±7.23
Calcium (mg/dL)	9.32±0.45	9.19±0.52	9.28±0.45	9.33±0.43	9.38±0.42	9.45±0.43
Bicarbonate (mEq/L)	27.72±2.81	27.50±3.17	27.75±2.86	27.78±2.75	27.74±2.68	27.65±2.67

(*continued*)

Table 1 (***Continued***)

Variable	Serum LDL (mg/dL)					
	Total	<70	70−<100	100−<130	130−<160	≥160
Glucose (mg/dL)	115.26±44.35	121.02±50.58	117.17±44.00	113.67±42.07	111.92±42.58	113.96±48.62
Hemoglobin (g/dL)	14.43±1.65	13.53±1.92	14.17±1.65	14.58±1.53	14.86±1.46	15.01±1.46
Hemoglobin A1c (%)	6.86±1.76	6.82±1.54	6.84±1.58	6.83±1.78	6.89±2.01	7.13±2.32
Sodium (mEq/L)	139.23±2.89	138.91±3.37	139.29±2.96	139.31±2.79	139.25±2.71	139.09±2.73
Potassium (mEq/L)	4.31±0.45	4.32±0.49	4.32±0.45	4.30±0.44	4.30±0.43	4.31±0.43
White Blood Cell Count ($\times 10^3/mm^3$)	7.22±2.76	7.36±3.46	7.20±2.83	7.17±2.63	7.22±2.55	7.35±2.44
Systolic blood pressure (mm Hg)	134.48±19.07	132.28±19.82	133.81±18.93	134.72±18.74	135.59±19.00	136.59±19.73
Diastolic blood pressure (mm Hg)	75.39±11.89	71.79±12.22	73.58±11.62	75.96±11.52	77.92±11.62	79.45±11.96
Body mass index (kg/m^2)	29.24±5.70	28.45±5.95	29.14±5.77	29.37±5.69	29.52±5.55	29.57±5.34
C-reactive protein (mg/L)	0.5 (0.2,1.2)	0.7 (0.3,2.9)	0.5 (0.2,1.2)	0.5 (0.2,1.1)	0.4 (0.2,0.9)	0.4 (0.2,0.9)
Lipid panel						
Triglycerides (mg/dL)	129 (88,192)	99 (68,152)	118 (81,177)	132 (91,194)	145 (102,211)	163 (116,236)
High density lipoprotein (mg/dL)	44.09±14.07	44.29±17.67	43.95±14.57	44.12±13.47	44.04±12.60	44.39±12.23
Total cholesterol (mg/dL)	180.84±42.01	124.59±25.79	154.04±18.59	184.99±17.97	217.02±18.35	262.58±34.10
Low density lipoprotein (mg/dL)	109.96±34.59	57.83±10.48	86.20±8.42	113.92±8.58	142.75±8.47	182.61±24.12
Medications						
Statin	649,353 (33%)	93,193 (46%)	283,114 (45%)	188,428 (30%)	59,792 (17%)	24,826 (15%)
Non-statin	110,338 (6%)	13,898 (7%)	37,875 (6%)	33,884 (5%)	16,360 (5%)	8,321 (5%)
Angiotensin-converting Enzyme inhibitor	644,315 (32.7%)	82,055 (41%)	241,463 (38%)	198,524 (31%)	86,280 (25%)	35,993 (22%)
Angiotensin II receptor blocker	80,199 (4.1%)	12,300 (6%)	32,926 (5%)	23,046 (4%)	8,734 (3%)	3,193 (2%)
Aspirin	142 (0.01%)	25 (0.01%)	53 (0.01%)	34 (0.01%)	17 (0.00%)	13 (0.01%)
β blockers	455,390 (23.1%)	66,376 (33%)	181,754 (29%)	132,033 (21%)	52,919 (15%)	22,308 (14%)
Calcium channel blockers	291,776 (14.8%)	36,446 (18%)	109,951 (17%)	90,645 (14%)	38,921 (11%)	15,813 (10%)
Diuretics	428,609 (21.7%)	56,121 (28%)	157,518 (25%)	132,125 (21%)	58,619 (17%)	24,226 (15%)
Glucose lowering	347,318 (17.6%)	55,115 (27%)	141,220 (22%)	97,326 (15%)	37,494 (11%)	16,163 (10%)
Clopidogrel	1,033 (0.05%)	264 (0.13%)	424 (0.07%)	237 (0.04%)	71 (0.02%)	37 (0.02%)

*Values are expressed as mean ± SD, median (interquartile range), or percentage, as appropriate. Percentages might not add up to 100% because of rounding.

risk lessened as CKD progressed in subjects with high LDL, whereas non-ASCVD hospitalization risk amplified as CKD progressed in both low and high LDL.

We have confirmed that, same as in the general population,[15] the association between higher cholesterol and higher risk of all-cause and CV mortality is present in patients with all stages of CKD. This association attenuated as CKD progressed in our findings, and could be accounted for by competing risk factors for death of all causes and CV death such as increased oxidative propensity.[16,17] In the previous literature, the association of LDL with mortality in patients with CKD has shown mixed results.[18−22] These studies may have been more limited in size or reported all stages of CKD combined.

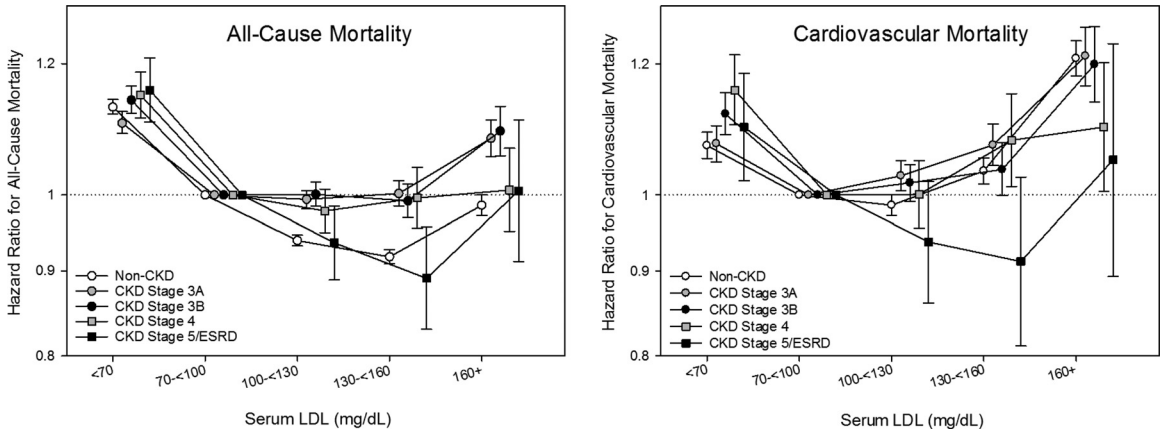

Figure 1. Association of Serum LDL (mg/dL) with *(A)* all-cause and *(B)* cardiovascular mortality stratified by CKD Stage in 1,972,851 veterans after full adjustment. *Adjusted for age, gender, race, ethnicity, smoking status, Charlson Comorbidity Index, myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, chronic pulmonary disease, dementia, liver disease, malignancy, diabetes mellitus, atrial fibrillation, hypertension, depression, ischemic heart disease, use of statin therapy, use of non-statin lipid-lowering drug therapy, BMI, albumin, high-density lipoproteins, triglycerides, systolic blood pressure, diastolic blood pressure, and medication use (angiotensin-converting enzyme inhibitor, angiotensin II receptor blocker, acetylsalicylic acid, beta-blockers, calcium channel blockers, diuretics, glucose-lowering medication, and clopidogrel).

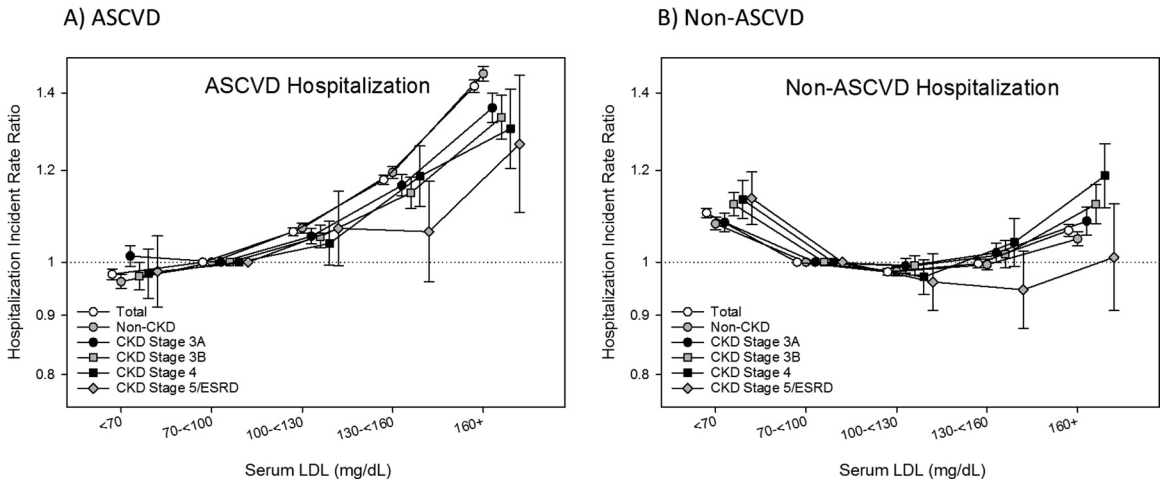

Figure 2. Association of Serum LDL (mg/dL) with *(A)* ASCVD and *(B)* non-ASCVD hospitalization incidence rate ratio stratified by CKD Stage in 1,972,851 veterans after full adjustment. *Adjusted for age, gender, race, ethnicity, smoking status, Charlson Comorbidity Index, myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, chronic pulmonary disease, dementia, liver disease, malignancy, diabetes mellitus, atrial fibrillation, hypertension, depression, ischemic heart disease, use of statin therapy, use of non-statin lipid-lowering drug therapy, BMI, albumin, high-density lipoproteins, triglycerides, systolic blood pressure, diastolic blood pressure, and medication use (angiotensin-converting enzyme inhibitor, angiotensin II receptor blocker, acetylsalicylic acid, beta-blockers, calcium channel blockers, diuretics, glucose-lowering medication, and clopidogrel).

Contrary to the expected causal relation between LDL and risk of atherosclerosis, we found an association between low LDL and mortality. However, this observation is in line with numerous other reports from cohorts of malnourished patients or patients with increased inflammation[23] and was reported for total cholesterol in veterans with CKD.[18] In our cohort we found an association of elevated mortality risk for lower LDL independent of age, cancer comorbidity, and CCI which includes most diseases associated with malnutrition.

Because of the paradoxical increase in CV mortality with low cholesterol we wanted to explore this association separating ASCVD and non-ASCVD and examined the risk of hospitalizations using a published definition.[24] This was done to separate the events likely to be reduced by statins from other CV events because LDL reduction by statins is expected to reduce CV mortality and morbidity only for ASCVD but not for non-ASCVD.

For ASCVD we observed a linear increase in hospitalizations for events with increasing LDL. In patients with high LDL, the higher rate of ASCVD events attenuated with the progression of CKD, similar to what was observed for mortality. Again, this is likely attributable to competing risk factors for ASCVD events. We hypothesized that low LDL would be associated with the higher mortality risk with the progression of CKD owing to the association of low LDL with the malnutrition-inflammation complex syndrome (MICS). We observed a lower ASCVD hospitalization risk in patients with low LDL and CKD progression. These data were not owing to patient attrition because

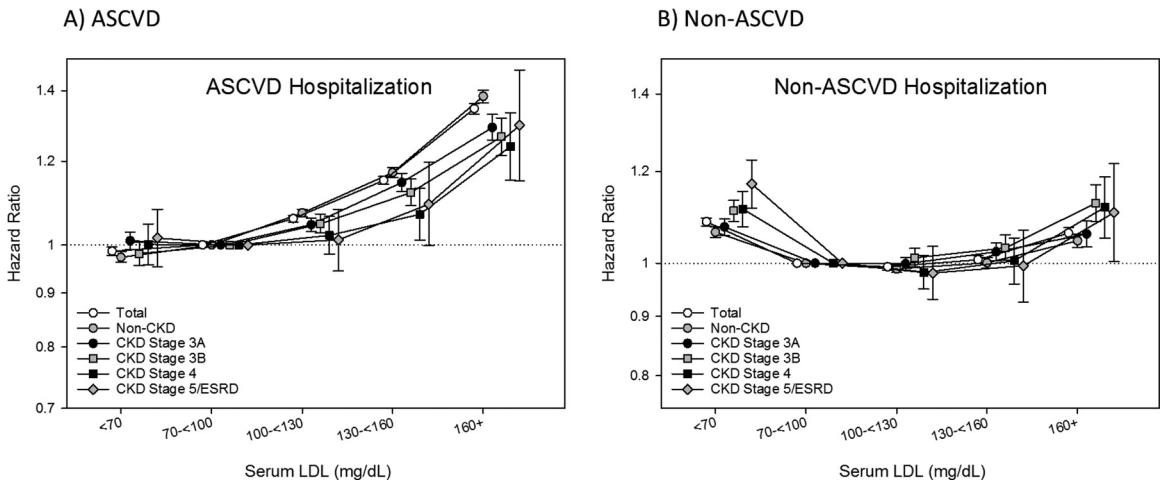

Figure 3. Association of Serum LDL (mg/dL) with *(A)* ASCVD and *(B)* non-ASCVD hospitalization stratified by CKD Stage in 1,972,851 veterans after full adjustment. *Adjusted for age, gender, race, ethnicity, smoking status, Charlson Comorbidity Index, myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, chronic pulmonary disease, dementia, liver disease, malignancy, diabetes mellitus, atrial fibrillation, hypertension, depression, ischemic heart disease, use of statin therapy, use of non-statin lipid-lowering drug therapy, BMI, albumin, high-density lipoproteins, triglycerides, systolic blood pressure, diastolic blood pressure, and medication use (angiotensin-converting enzyme inhibitor, angiotensin II receptor blocker, acetylsalicylic acid, beta-blockers, calcium channel blockers, diuretics, glucose-lowering medication, and clopidogrel).

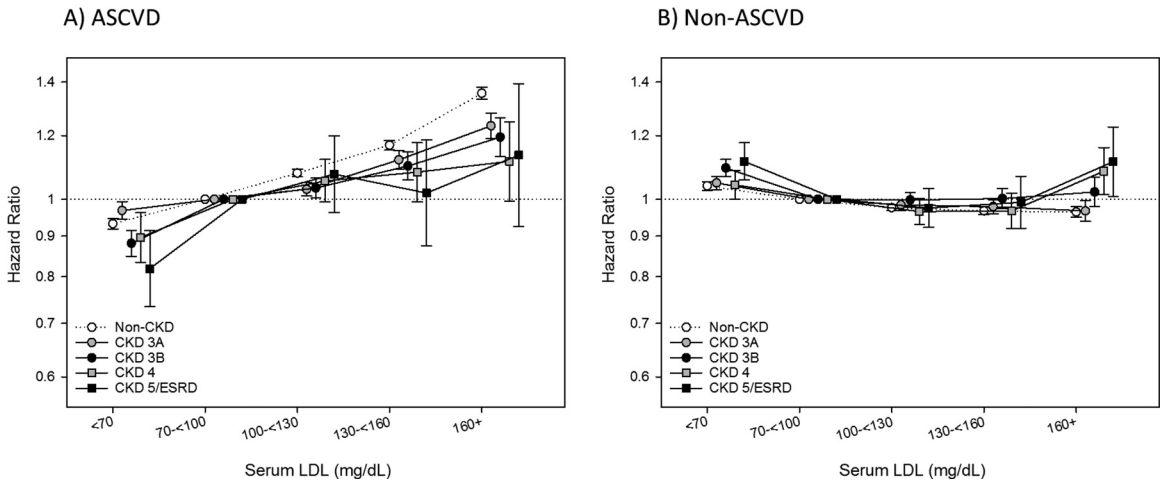

Figure 4. Competing risk regression analyses of association of Serum LDL (mg/dL) with *(A)* ASCVD and *(B)* non-ASCVD hospitalization stratified by CKD Stage in 1,972,851 veterans after full adjustment. *Adjusted for age, gender, race, ethnicity, smoking status, Charlson Comorbidity Index, myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, chronic pulmonary disease, dementia, liver disease, malignancy, diabetes mellitus, atrial fibrillation, hypertension, depression, ischemic heart disease, use of statin therapy, use of non-statin lipid-lowering drug therapy, BMI, albumin, high-density lipoproteins, triglycerides, systolic blood pressure, diastolic blood pressure, and medication use (angiotensin-converting enzyme (ACE) inhibitor, angiotensin II receptor blocker (ARB), acetylsalicylic acid (ASA), beta-blockers, calcium channel blockers, diuretics, glucose-lowering medication, and clopidogrel).

competing risk analysis showed a similar to even lower risk with CKD progression. The data show that with the progression of CKD and presumably increased rate of MICS paralleling it,[24] lower LDL overcomes an expected increased risk of ASCVD events and is associated with a lower risk of ASCVD hospitalization. Although one might expect that low LDL in progressive CKD is observed owing to CKD-MICS and LDL would not be causally related to ASCVD to the same extent as in patients without CKD, our data contradicts this assumption and show that low LDL might still be "protective" against ASCVD.

The association of LDL with non-ASCVD hospitalizations was U shaped, similar to what is observed for total and CV mortality. On the one hand, it is possible, that some conditions included in the non-ASCVD hospitalization definition were still related to previous ASCVD, as for example, coronary artery disease can lead to heart failure, and therefore, non-ASCVD hospitalizations might be also indirectly affected by a higher LDL level. In contrast, low LDL may not be protective against non-ASCVD related conditions in the same way as for ASCVD-related hospitalizations and low LDL may serve as a marker of malnutrition, rather than a causally related factor to increased non-ASCVD hospitalizations. The association of low LDL with non-ASCVD events could be related to a higher risk of arrhythmia and sudden death owing to MICS resulting in increased vascular stiffness and calcification and ultimately in increased BP and increased hemorrhagic stroke and heart failure.[25,26]

Effect modification by CKD on associations of LDL with CV outcomes reported by us are consistent with results from the Study of Heart and Renal Protection (SHARP) trial.[38] A large meta-analysis[39] including 48,429 patients with CKD across 31 randomized controls trials investigating the impact of statin on major clinical outcomes found a 23%, 18%, and 9% reduction in major cardiovascular events, coronary events, and cardiovascular or all-cause death, respectively. In their study, the associations were incrementally attenuated as CKD stage progressed, however, associations were not separately evaluated for ASCVD and non-ASCVD outcomes.

Our study has a number of strengths. In addition to being one of the largest studies to explore the relationship between LDL and cardiovascular outcomes across CKD strata, our results showed consistent findings across strata of statin use, age, CCI, and cancer. The large cohort size and wealth of VA data allow us to adjust for a number of potential confounders and examine associations across CKD strata and across subgroups.

Although there is a plethora of available data for this observational cohort study, we cannot rule out residual confounding nor make causal inferences. We were unable to adjust for markers of nutrition or apolipoproteins that could be potential confounders. Data on critical inflammatory markers were highly missing for this cohort. Our sources for outcomes were administrative electronic medical records and there remains possible outcome misclassification. However, we restricted our hospitalization event outcomes to primary or secondary International Classification of Diseases codes to only obtain adverse events and minimize these possible biases. In addition, it is unknown to what extent is the lower LDL observed owing to malnutrition, inflammation, and comorbidities rather than clinical lipid management. Finally, our results may not be generalizable to the general population given that our source cohort of VA patients is primarily comprised of older men with multiple comorbidities.

In conclusion, LDL could be used as a predictive risk factor for ASCVD events in all stages of CKD, which is in line with KDIGO recommendations for cholesterol lowering[27] and our previously published observations in predialysis and early dialysis,[28,29] Similar associations were not observed in advanced stages of CKD. Further studies are needed to determine important correctable risk factors for

cardiovascular outcomes in patients with CKD as the pathogenesis of cardiovascular disease in patients with more advanced kidney disease may differ from those with normal kidney function.

Disclosures

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Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2022.01.034.

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