Association between LDL-C and Risk of Myocardial Infarction in CKD

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ABSTRACT

LDL cholesterol (LDL-C) is an important marker of coronary risk in the general population, but its utility in people with CKD is unclear. We studied 836,060 adults from the Alberta Kidney Disease Network with at least one measurement of fasting LDL-C, estimated GFR (eGFR), and proteinuria between 2002 and 2009. All participants were free of stage 5 CKD at cohort entry. We followed participants from first eGFR measurement to March 31, 2009; we used validated algorithms applied to administrative data to ascertain primary outcome (hospitalization for myocardial infarction) and Cox regression to calculate adjusted hazard ratios (HRs) for myocardial infarction by LDL-C categories within eGFR strata. During median follow-up of 48 months, 7762 patients were hospitalized for myocardial infarction, with incidence highest among participants with the lowest eGFR. Compared with 2.6–3.39 mmol/L (referent), the risk associated with having LDL-C above 4.9 mmol/L seemed greatest for GFR≥90 ml/min per 1.73 m^2 and least for eGFR=15–59.9 ml/min per 1.73 m^2. Specifically, the adjusted HRs (95% confidence intervals) of myocardial infarction associated with LDL-C of ≥4.9 compared with 2.6–3.39 mmol/L in participants with eGFR=15–59.9, 60–89.9, and ≥90 ml/min per 1.73 m^2 were 2.06 (1.59, 2.67), 2.30 (2.00, 2.65), and 3.01 (2.46, 3.69). In conclusion, the association between higher LDL-C and risk of myocardial infarction is weaker for people with lower baseline eGFR, despite higher absolute risk of myocardial infarction. Increased LDL-C may be less useful as a marker of coronary risk among people with CKD than the general population.

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People with CKD are at high risk of coronary disease, and the risk of adverse cardiovascular outcomes rises sharply at lower levels of estimated GFR (eGFR).[1,2] Although dyslipidemia is common in CKD populations, LDL cholesterol (LDL-C) levels do not reliably identify hemodialysis patients who are at the highest risk for coronary events[3]—in contrast to the situation in the general population, in which LDL-C is a key risk factor for coronary events.

The prevalence of less severe forms of CKD is much higher than the prevalence of kidney failure,[4] and coronary disease is a major cause of morbidity and mortality in nondialysis-dependent CKD.[2] However, much less is known about the association between LDL-C and coronary risk in this population. Because current guidelines advise that LDL-C should be used to select people with nondialysis-dependent CKD for lipid-lowering treatment,[5] this issue is clinically important.

We used data from a large population of people who were treated in a universal health care system to examine the association between LDL-C and the

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risk of first myocardial infarction during follow-up after excluding those individuals with stage 5 CKD at baseline. Given the lack of exponential association between LDL-C and coronary risk in hemodialysis patients, we hypothesized that the excess risk associated with higher LDL-C would be attenuated in people with CKD.

RESULTS

Study flow is shown in Supplemental Figure 1, and baseline characteristics of the 836,060 participants are shown in Table 1. Overall, the proportions of participants in the <2.6, 2.6–3.39, 3.4–4.09, 4.1–4.89, and ≥4.9 mmol/L LDL-C categories were 28%, 36%, 23%, 10%, and 3%, respectively (Figure 1). The median days between the index date and the nearest LDL-C value were 0 (interquartile range [IQR]=0, 0; range=−6, +6 months). The mean (SD) eGFR was 90.1 (18.3) ml/min per 1.73 m^2. During follow-up, 21,732 (2.6%) and 928 (0.1%) individuals died and experienced ESRD, respectively.

During median follow-up of 48 months (range=1 day to 83 months), 7762 patients were hospitalized for myocardial infarction (Table 2). The unadjusted rate of myocardial infarction among participants with eGFR=15–59.9 ml/min per 1.73 m^2 and LDL-C<2.6 mmol/L was higher than among those participants with eGFR≥90 ml/min per 1.73 m^2 and LDL-C≥4.9 mmol/L (9.7 versus 3.1 per 1000 patient-years, $P<0.001$).

Compared with a referent category of 2.6–3.39 mmol/L, the multivariable adjusted excess risk (hazard ratio [HR]) associated with levels of LDL-C above 4.9 mmol/L seemed greatest for GFR≥90 ml/min per 1.73 m^2 and least for levels of 15–59.9 ml/min per 1.73 m^2 (Table 3). When examined using a restricted cubic spline, these results suggested that the relation between LDL-C and the risk of myocardial infarction was linear at LDL-C above 2.6 mmol/L (data not shown). Therefore, we fit an additional Cox model for the relation between LDL-C and the risk of myocardial infarction, treating both LDL-C and eGFR as continuous variables. This model showed that the HRs (95% confidence intervals [CIs]) of myocardial infarction associated with each 1 mmol/L increase in LDL-C above 2.6 mmol/L are 1.48 (1.43, 1.54), 1.33 (1.27, 1.40), 1.26 (1.18, 1.35), 1.20 (1.09, 1.3), and 1.13 (1.01, 1.27) among people with eGFR of 90, 60, 45, 30, and 15 ml/min per 1.73 m^2 respectively (Figure 2).

Table 1. Demographic and clinical characteristics of participants

	All Participants (*n*=836,060)	Baseline eGFR (ml/min per 1.73 m^2)		
		15–59.9 (*n*=47,092)	60–89.9 (*n*=351,849)	≥90 (*n*=437,119)
Age[a] (yr)	49.4 (14.8)	70.5 (11.5)	55.6 (12.9)	42.1 (11.8)
LDL-C[a] (mmol/L)	3.1 (0.9)	3.1 (0.9)	3.2 (0.9)	3.0 (0.9)
LDL-C (mmol/L)				
<2.6	28	31	24	32
2.6–3.39	36	34	35	36
3.4–4.09	23	22	25	21
4.1–4.89	10	10	12	9
≥4.9	3	3	3	2
Women	50	55	47	52
Aboriginal status	1	1	1	2
Socioeconomic status				
Low	9	4	7	10
Social assistance	2	2	2	3
Diabetes	8	22	9	7
Hypertension	23	66	29	14
eGFR (ml/min per 1.73 m^2)[b]	91 (78, 103)	53 (45, 57)	79 (72, 85)	102 (96, 110)
Proteinuria				
None	91	78	91	92
Mild	8	16	8	7
Heavy	1	6	1	1
Charlson comorbidities				
Cancer	3	7	3	2
CVD	2	7	2	1
CHF	1	8	1	0
Chronic lung disease	12	17	12	11
Dementia	0	2	0	0
Metastatic solid tumor	0	1	0	0
Myocardial infarction	2	7	2	1
Mild liver disease	1	1	1	1
Moderate/severe liver disease	0	0	0	0
Paraplegia	0	1	0	0
Peptic ulcer disease	2	3	2	2
Peripheral vascular disease	1	5	1	0
Rheumatic disease	1	2	1	1
Medication use[c]				
Statin	17	29	18	8
ACE inhibitor or ARB	23	46	23	10
β-blocker	10	23	10	4
Fibrate or ezetimibe	2	6	2	1

Data expressed as percent except where noted. Totals do not always add to 100% because of rounding. Proteinuria defined as none (ACR<30 mg/g or urine dipstick negative), mild (ACR=30–300 mg/g or urine dipstick trace or 1+), or heavy (ACR>300 mg/g or urine dipstick≥2+). Low socioeconomic status was defined by annual family income<$39,250 CAD, and receiving social assistance was based on government of Alberta health care insurance records. CVD, cerebrovascular disease; CHF, congestive heart failure; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker.
[a]Mean (SD).
[b]Median (interquartile range).
[c]Among the 273,540 individuals with data available on medication use, 40,611 individuals had eGFR=15–59.9, 155,315 individuals had eGFR=60–89.9, and 77,614 individuals had eGFR≥90 ml/min per 1.73 m^2.

Sensitivity Analyses: Only Participants with Data on Medication Use

When analyses were restricted to the subset of 273,540 participants with medication data, results were similar to the primary analysis. Specifically, the adjusted HRs (95% CIs) of myocardial infarction associated with LDL-C≥4.9 mmol/L compared with LDL-C=2.6–3.4 mmol/L in participants with eGFR values of 15–59.9, 60–89.9, and ≥90 ml/min per 1.73 m^2 were 1.96 (1.49, 2.58), 1.92 (1.60, 2.30), and 2.44 (1.73, 3.43), respectively.

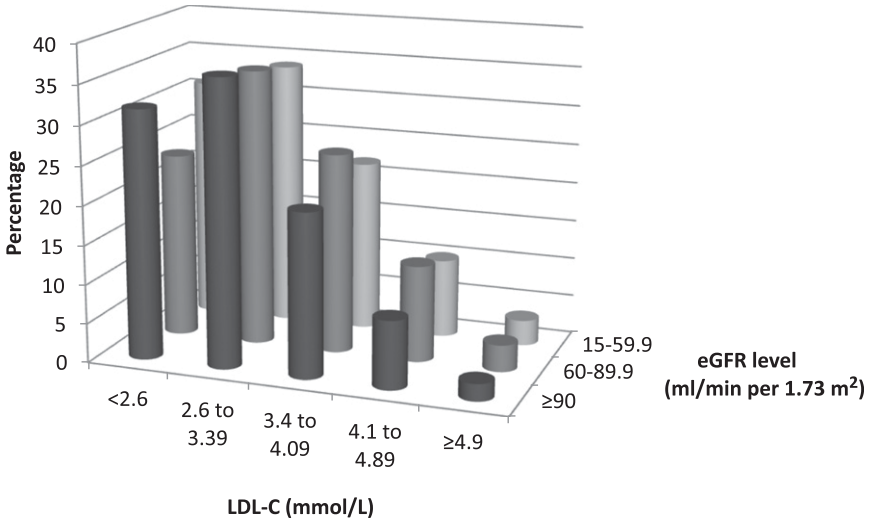

Figure 1. Prevalence of LDL-C categories by eGFR level. The figure shows that a higher proportion of participants with eGFR≥90 ml/min per 1.73 m^2 had LDL-C<2.6 mmol/L, as compared to those with lower levels of eGFR.

Sensitivity Analyses: ST Segment Elevation Myocardial Infarction as the Outcome of Interest

The proportions of individuals experiencing a first ST segment elevation myocardial infarction (STEMI) during follow-up were 0.9%, 0.4%, and 0.2% compared with 3.6%, 1.2%, and 0.4% experiencing all types of myocardial infarction for eGFR of 15–59.9, 60–89.9, and ≥90 ml/min per 1.73 m^2, respectively. Results of analyses examining the risk of STEMI as a function of LDL-C were similar to those results in the primary analysis. Specifically, the HRs (95% CIs) of STEMI associated with LDL-C of ≥4.9 mmol/L compared with LDL-C of 2.6–3.4 mmol/L in participants with eGFR of 15–59.9, 60–89.9, and ≥90 ml/min per 1.73 m^2 were 2.32 (1.47, 3.68), 2.28 (1.81, 2.87), and 3.29 (2.40, 4.51), respectively.

Other Sensitivity Analyses

Results were similar when LDL, eGFR, and statin use were treated as time-varying variables (Supplemental Table 1); statin use was defined based on a prescription within 90 days of the index date (Supplemental Table 2); individuals with a history of myocardial infarction at baseline were excluded (Supplemental Table 3); and we included individuals without a proteinuria measurement (Supplemental Table 4).

Table 2. Unadjusted incidence and rates of myocardial infarction by level of LDL-C for eGFR subgroups

LDL-C Category (mmol/L)	eGFR=15–59.9 ml/min per 1.73 m^2 (*n*=47,092)	eGFR=60–89.9 ml/min per 1.73 m^2 (*n*=351,849)	eGFR≥90 ml/min per 1.73 m^2 (*n*=437,119)
<2.6			
N (% within each column) with myocardial infarction	579 (1.2%)	1059 (0.3%)	442 (0.1%)
Unadjusted rate (95% CI) of myocardial infarction per 1000 patient-years	9.7 (8.9, 10.5)	3.4 (3.2,3.6)	1.0 (0.9, 1.1)
2.6–3.39			
N (% within each column) with myocardial infarction	535 (1.1%)	1333 (0.4%)	543 (0.1%)
Unadjusted rate (95% CI) of myocardial infarction per 1000 patient-years	7.8 (7.1, 8.4)	2.7 (2.6, 2.9)	1.0 (0.9, 1.1)
3.4–4.09			
N (% within each column) with myocardial infarction	340 (0.7%)	1042 (0.3%)	466 (0.1%)
Unadjusted rate (95% CI) of myocardial infarction per 1000 patient-years	7.6 (6.8, 8.5)	2.9 (2.7, 3.1)	1.4 (1.3, 1.5)
4.1–4.89			
N (% within each column) with myocardial infarction	182 (0.4%)	532 (0.2%)	306 (0.1%)
Unadjusted rate (95% CI) of myocardial infarction per 1000 patient-years	8.8 (7.6, 10.2)	3.0 (2.8, 3.3)	2.1 (1.9, 2.3)
≥4.9			
N (% within each column) with myocardial infarction	64 (0.1%)	225 (0.06%)	114 (0.03%)
Unadjusted rate (95% CI) of myocardial infarction per 1000 patient-years	9.9 (7.7, 12.6)	4.5 (4.0, 5.2)	3.1 (2.6, 3.7)

DISCUSSION

The discovery that LDL-C is directly and independently associated with risk of cardiovascular events[6] was a key factor in the development of cholesterol-lowering medications such as statins.[7] Patients with kidney failure are a notable exception to the general rule that patients with higher LDL-C levels are at the highest risk of cardiovascular events: it has been known for more than 30 years that low cholesterol is associated with adverse outcomes in hemodialysis populations.[8] Recent work has suggested that this result is caused by confounding by malnutrition and inflammation (themselves putative mediators of cardiovascular risk) in people with the lowest cholesterol levels.[3,9,10] These observations have led to speculation that this reverse epidemiology[11] contributes to the disappointing clinical benefits of statin treatment in dialysis populations.[12]

In this study of over 800,000 people without kidney failure, we examined the relation between LDL-C and hospitalization for myocardial infarction in strata defined by eGFR. Although higher levels of LDL-C were associated with higher risk for all three eGFR strata, the excess risk associated with markedly elevated LDL-C seemed largest for participants with baseline eGFR≥90 ml/min per 1.73 m^2 and lowest for participants with eGFR=15–59.9 ml/min per 1.73 m^2. The risk of myocardial infarction in this latter group as a function of LDL-C was notably flatter than for the group with unequivocally normal eGFR. Together with the findings of previous studies done in dialysis

Table 3. Adjusted HRs of myocardial infarction for eGFR subgroups

LDL-C Category (mmol/L)	HR (95% CI)		
	eGFR=15–59.9 ml/min per 1.73 m^2 (*n*=47,092)	eGFR=60–89.9 ml/min per 1.73 m^2 (*n*=351,849)	eGFR≥90 ml/min per 1.73 m^2 (*n*=437,119)
<2.6	0.93 (0.82, 1.04)	0.93 (0.85, 1.01)	0.98 (0.87, 1.12)
2.6–3.39	1.00	1.00	1.00
3.4–4.09	1.22 (1.06, 1.39)	1.20 (1.11, 1.30)	1.35 (1.19, 1.52)
4.1–4.89	1.68 (1.42, 1.99)	1.39 (1.26, 1.54)	1.99 (1.73, 2.29)
≥4.9	2.06 (1.59, 2.67)	2.30 (2.00, 2.65)	3.01 (2.46, 3.69)

Referent category is LDL-C=2.6–3.39. Adjusted for age, sex, diabetes, hypertension, Aboriginal status, socioeconomic status, proteinuria categories, statin use, and Charlson comorbidities (cancer, cerebrovascular disease, congestive heart failure, chronic pulmonary disease, dementia, metastatic solid tumor, myocardial infarction, liver disease, hemiplegia/paraplegia, peptic ulcer disease, peripheral vascular disease, and rheumatic disease).

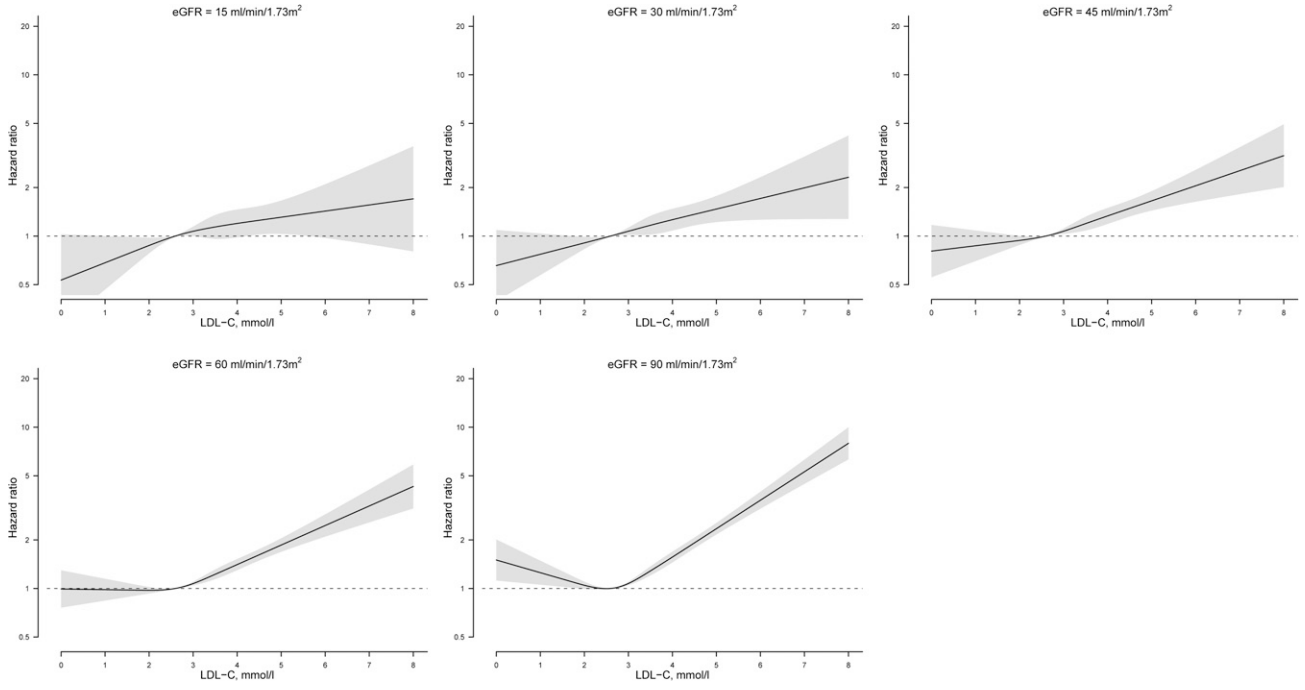

Figure 2. Adjusted relation between LDL-C and HR of myocardial infarction by eGFR as a continuous variable. LDL-C was modeled by a restricted cubic spline with four knots at the 5th, 35th, 65th, and 95th percentiles, corresponding to LDL-C values of 1.8, 2.8, 3.4, and 4.6 using a Cox regression model. The LDL value of 2.6 mmol/L was used as the referent. Because eGFR was treated as a continuous variable, we selected eGFR values of 15, 30, 45, 60, and 90 to show the splines. Fully adjusted for age, sex, diabetes, hypertension, Aboriginal status, socioeconomic status, proteinuria categories, statin use, and Charlson comorbidities (cancer, cerebrovascular disease, congestive heart failure, chronic pulmonary disease, dementia, metastatic solid tumor, myocardial infarction, liver disease, hemiplegia/paraplegia, peptic ulcer disease, peripheral vascular disease, and rheumatic disease).

populations, these data highlight the potential limitations of LDL-C as a predictor of coronary risk in people with advanced CKD.

Current practice emphasizes the value of LDL-C for identifying patients who will benefit from statin treatment as a therapeutic target, with lower LDL-C goals assigned to patients at highest risk.[13] Although there is debate about the merits of this approach, most major practice guidelines for the general population base the decision to initiate statin treatment (and subsequent dose adjustments) at least partially on LDL-C levels, which serve as a proxy for cardiovascular risk. We found that the rate of myocardial infarction among participants with eGFR=15–59.9 ml/min per 1.73 m^2 and the lowest levels of LDL-C was higher than among those participants with eGFR≥90 ml/min per 1.73 m^2 and the highest levels of LDL-C. Together with our previous work showing that the risk of myocardial infarction is similar among patients with CKD and patients with diabetes,[14] this result argues in favor of a more liberal approach to the use of statins in CKD populations. Specifically, rather than restricting the use of statins to CKD patients with elevated LDL-C, consideration should be given to treating CKD as a coronary risk equivalent, which is currently the case for diabetes. Although statins seem less effective in patients treated with dialysis than those patients with nondialysis-dependent CKD,[15] the results of the Study of Heart and Renal Protection found no evidence that the effectiveness of simvastatin/ezetimibe varied by baseline eGFR (P for heterogeneity across eGFR categories=0.73),[16] suggesting that more liberal use of statin-based regimens would likely improve outcomes for all people with nondialysis-dependent CKD.

Why would the association between LDL-C and the risk of myocardial infarction be weaker in people with nondialysis-dependent CKD than the general population? Because the prevalence of malnutrition and markers of inflammation increase as GFR declines,[17] the risk of coronary events in CKD patients with lower LDL-C may be influenced by these nontraditional coronary risk factors. The explanation for the attenuated coronary risk at higher LDL-C is less clear but may relate to other nontraditional mechanisms for coronary disease in the setting of advanced kidney disease or the competing risks of noncoronary cardiovascular events such as sudden cardiac death.[18] Either way, because the link between higher LDL-C and coronary events is attenuated in patients with CKD (and conversely, event rates among people with CKD and low or low-normal LDL-C are markedly higher than in the general population), it does not seem rational to base the indication for statin treatment in this population on LDL-C levels. Given the high coronary risk and the high case fatality rate associated with myocardial infarction in people with nondialysis-dependent CKD—as well as evidence that lipid-lowering therapy is beneficial[16,19,20]—consideration could be given to broad prescription of statins to this population rather than the current LDL-based thresholds for treatment.[21]

Previous studies examining the link between serum cholesterol and the risk of adverse outcomes in people with nondialysis-dependent CKD have reached contradictory results. One study (n=807)[22] showed that higher levels were associated with incident coronary events. One study showed that lower levels were associated with cardiovascular mortality (n=986).[23] One study (n=5808)[24] showed no association between cholesterol and cardiovascular mortality. Although all three studies were rigorously done, their relatively small sample sizes may have limited the strength of their conclusions, especially for people with eGFR=15–30 ml/min per 1.73 m^2 who were relatively infrequent in all three studies. Our data suggest that the prognostic power of LDL-C for myocardial infarction is attenuated at lower levels of kidney function. Whether this observation is because of increased likelihood of effect modification by inflammation and malnutrition at lower levels of kidney function will require additional study in datasets that include this information in a well characterized population of people with advanced CKD.

Our study has important strengths, including its large size, population-based design, and rigorous statistical methods. However, our study also has several limitations that should be considered when interpreting results. First, we based myocardial infarction rates on claims and hospitalization data rather than patient interviews. However, we used validated algorithms to ascertain this outcome, and there is no obvious reason why misclassification from such algorithms would have systematically varied between patients with and without CKD. In addition, results were similar when considering the most severe subset of myocardial infarction (STEMI). Therefore, this limitation is unlikely to have influenced our findings. Second, we did not have data on nutritional status or markers of inflammation (such as C-reactive protein or IL-6), and thus, we cannot confirm our hypothesis that the higher risk among participants with lower eGFR was caused by a higher prevalence of malnutrition and biochemical inflammation. Future studies should measure such parameters in a large cohort of patients with advanced nondialysis-dependent CKD. Third, despite the large number of participants in our study, the low number with myocardial infarction in some strata may have reduced our statistical power, especially for participants with the lowest eGFR, where CIs were broader, thus permitting less confidence in the point estimates for the risk associated with LDL-C. Fourth, because we studied only people treated in a single Canadian province, generalizability of these results to different settings will require confirmation. Fifth, we adjusted for use of statins in all analyses and a number of other medications that might have influenced LDL-C levels or cardiovascular risk (including fibrates and ezetimibe) in sensitivity analysis. Unfortunately, medication data were only available for 33% of the study cohort who were insured by the provincial drug plan, and thus, the primary analysis used a dummy variable for statin use missing in the remainder. However, results were similar in sensitivity analyses that were restricted to the subset of 273,540 participants with complete

data. Although it is possible that the missing data on medication use have led to bias, statin use is less common in people with CKD than otherwise similar people. This result suggests that complete data on medication use would have strengthened our conclusions.

In conclusion, we found that the association between LDL-C and the risk of myocardial infarction was present for all three eGFR strata but seems weaker in the presence of CKD. Therefore, LDL-C may be less useful as a marker of coronary risk among people with advanced nondialysis-dependent CKD than it is in the general population.

CONCISE METHODS

Alberta Kidney Disease Network Database

We used the Alberta Kidney Disease Network population-based database[25] (Supplemental Figure 1) to identify adults (n=2,004,791) 18 years of age and older with at least one outpatient measurement of serum creatinine done in Alberta between 2002 and 2009 who were free of stage 5 CKD (*i.e.*, had eGFR≥15 ml/min per 1.73 m^2 and not treated with dialysis or kidney transplantation). To avoid confounding by receipt of dialysis and/or immunosuppressive medications and because the association between LDL-C and adverse outcomes has already been documented for dialysis patients, we excluded people with stage 5 CKD at baseline.

The first available serum creatinine and the corresponding date were set as the index serum creatinine and index date, respectively. We used the Chronic Kidney Disease Epidemiology Collaboration equation[26] and a standardized serum creatinine assay to estimate the baseline eGFR for each participant. We excluded people with index eGFR<15 ml/min per 1.73 m^2 before cohort entry and people treated with dialysis or kidney transplantation (ascertained by linkage to the provincial renal programs and not dependent on serum creatinine data). Of the remainder, 836,060 (41.7%) had at least one measurement of proteinuria (dipstick urinalysis or albumin to creatinine ratio [ACR]) obtained within 6 months of the index creatinine value and a baseline LDL-C measurement (obtained within 6 months of the index creatinine value). For individuals with multiple measurements of proteinuria and LDL-C during this 1-year period, the median value was chosen. Demographic data and socioeconomic status for Alberta Kidney Disease Network participants were determined from the provincial health ministry.[27] Data on medication use were available for 273,540 (33%) participants with insurance from the provincial public drug plan. Individuals covered by the drug plan included all those participants ages≥65 years (n=132,334) plus an additional 141,206 people ages<65 years who we identified as having coverage based on a reimbursed claim for any medication during follow-up. We classified use/nonuse status for statins, fibrates, ezetimibe, β-blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers. Individuals were considered to be users if they had at least one prescription in the year before the index date. For individuals without data on medication use, we modeled use of these medications with a dummy variable to represent unknown status. Proteinuria was defined as none (ACR<30 mg/g or urine dipstick negative), mild (ACR=30–300 mg/g or urine dipstick trace or 1+), or heavy (ACR>300 mg/g or urine dipstick≥2+). ACR was used as the primary measure of proteinuria, and if unavailable, it was supplemented by dipstick urinalysis.

Definitions

Routine protocol for clinical laboratories in Alberta is to perform LDL-C measurements only in patients who indicate that they have been fasting for >6 hours at the time of blood collection; data on duration of fasting of participants were not available. We categorized LDL-C into five categories based on the ATP III classification of LDL: <2.6, 2.6–3.39, 3.4–4.09, 4.1–4.89, and ≥4.9 mmol/L (to convert LDL-C millimoles per liter to milligrams per deciliter, divide by 0.02586).

Ascertainment of Outcomes

Participants were followed from their index date until the study end (March 31, 2009). The study outcome was first hospitalization for myocardial infarction during follow-up. Individuals were censored at death but not ESRD. We used a previously validated algorithm based on hospitalization data from 1994 to 2009 to identify participants with myocardial infarction during follow-up.[28] The algorithm was based on most responsible International Classification of Diseases-10 codes I21 (acute transmural and subendocardial myocardial infarctions of the anterior or inferior walls and other and unspecified sites) and I22 (subsequent myocardial infarctions of the anterior or inferior walls and other and unspecified sites). In sensitivity analyses, we examined the subset of myocardial infarction that was associated with ST segment elevation by restricting the International Classification of Diseases-10 codes to I21.0, I21.1, I21.2, and I21.3. Participants with a history of myocardial infarction (*i.e.*, before baseline) were included.

Statistical Analyses

The primary analysis used Cox regression to calculate adjusted HRs of myocardial infarction during follow-up by LDL-C categories in each eGFR stratum by including a two-way interaction term. eGFR categories were defined as 15–59.9, 60–89.9, and ≥90 ml/min per 1.73 m^2. HRs were calculated using the LDL-C=2.6–3.39 mmol/L category as the referent. To further explore the association between LDL-C and myocardial infarction, LDL-C was modeled by a restricted cubic spline with knots at the 5th, 35th, 65th, and 95th percentiles.[29] The Cox proportional hazards assumption was tested by visually examining the log–log survival plots. The fully adjusted Cox models included baseline age, sex, diabetes, hypertension, proteinuria, Aboriginal status, socioeconomic status, statin use, and comorbidities (cancer, cerebrovascular disease, congestive heart failure, chronic pulmonary disease, dementia, metastatic solid tumor, myocardial infarction, liver disease, hemiplegia/paraplegia, peptic ulcer disease, peripheral vascular disease, and rheumatic disease) assessed by validated algorithms based on claims and hospitalization data.[30] All models were adjusted for statin use at baseline. We also used unadjusted Poisson regression to calculate the rate of myocardial infarction per 1000 patient years of follow-up in each GFR stratum and within LDL-C categories for each GFR stratum. We did seven additional sets of sensitivity analyses to show the robustness of our findings. First, we additionally adjusted for use of angiotensin-converting

enzyme inhibitors, angiotensin receptor blockers, β-blockers, fibrates, and ezetimibe. Results were similar to the primary analysis and are not presented further. Second, we repeated analyses in the subset of 273,540 (33%) participants with data on medication use. Third, we repeated the primary analyses and calculated adjusted HRs using Cox regression and the same set of predictors for the outcome of STEMI during follow-up. Other sensitivity analyses repeating the main analyses were as follows. We used time-varying variables for LDL, eGFR, and statin use, all evaluated annually at the anniversary of cohort entry. We defined statin use based on a prescription within 90 days of the index date. We excluded individuals with a history of myocardial infarction at baseline, and we included individuals without a proteinuria measurement.

We did analyses using Stata 11 MP software (www.stata.com) and R (The R Project for Statistical Computing; www.r-project.org). The institutional review boards of the Universities of Calgary and Alberta approved the study.

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DISCLOSURES

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