Relation of Cardiovascular Events and Deaths to Low-Density Lipoprotein Cholesterol Level Among Statin-Treated Patients With Atherosclerotic Cardiovascular Disease

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This study describes subsequent cardiovascular events and deaths by low-density lipoprotein cholesterol (LDL-C) level in patients with atherosclerotic cardiovascular disease (ASCVD) receiving moderate- to high-intensity statins. Olmsted County, Minnesota residents with index ASCVD (myocardial infarction, unstable angina, coronary revascularization, ischemic stroke or transient ischemic attack) occurring between 2005 and 2012 were identified, and those with a prescription for a moderate- or high-intensity statin and an LDL-C measurement in the 90 days after index were included. Cox regression models were used to examine associations between LDL-C, modeled as a time-dependent variable, and a composite outcome of subsequent cardiovascular events or all-cause death. Among 1,854 patients with ASCVD (mean [SD] age 66.0 [13.3] years, 63.6% male), a total of 1,241 events were observed from index ASCVD through follow-up (median of 5.9 years). The rate (95% confidence interval) per 100 person-years was 11.26 (10.64 to 11.91). Starting follow-up 90 days after index ASCVD event, the rates per 100 person-years were 10.51 (9.57 to 11.52), 9.57 (8.66 to 10.55), and 11.40 (9.96 to 12.98) for LDL-C <70, 70-<100 and ≥100 mg/dl, respectively. After adjustment for age, sex, and previous diagnoses of ASCVD, diabetes, hypertension, heart failure, and chronic kidney disease, the hazard ratio for cardiovascular event and/or death was significantly higher for patients with LDL-C ≥100 mg/dl than those with LDL-C <70 mg/dl (1.31 [1.08 to 1.59]). In conclusion, in patients with ASCVD, subsequent cardiovascular events occur at a high rate and the rates are highest in patients with LDL-C ≥100 mg/dl suggesting unmet treatment needs even in patients receiving moderate- to high-intensity statins. **(Am J Cardiol 2019;123:1739−1744)**

Cardiovascular disease (CVD) is the leading cause of mortality worldwide[1] despite a plethora of available treatments including agents such as statins and PCSK9 inhibitors that reduce low-density lipoprotein cholesterol (LDL-C), a well-established CVD risk factor.[1−4] Although LDL-C reducing agents have been shown to be efficacious, many trials have indicated that while treating to LDL-C targets improves cardiovascular (CV) outcomes, lowering LDL-C beyond previous targets provides even greater benefit.[2,5,6] However, limited information outside of the clinical trial setting is available to determine whether CV event rates remain high even when LDL-C is controlled in real-world populations. This study describes subsequent CV disease burden by LDL-C level in patients with atherosclerotic cardiovascular disease (ASCVD) who were prescribed moderate- to high-intensity statins in an observational community setting.

Methods

This study was conducted in Olmsted County, Minnesota, utilizing the resources of the Rochester Epidemiology Project (REP), a records-linkage system which includes virtually complete capture of health care utilization and outcomes in county residents.[7−10] The REP encompasses more than 6 million person-years of follow-up in over 500,000 unique individuals since 1966.[7] Due to the relative geographic isolation of Olmsted County and because only a few providers (including Mayo Clinic and its 2 affiliated hospitals and Olmsted Medical Center and its affiliated hospital) deliver the vast majority of health care to local residents, the capture of nearly all care delivered to local residents is possible. Furthermore, demographic and ethnic characteristics of Olmsted County are representative of the state of Minnesota and the Midwest region of the United States, supporting the generalizability of REP data.[8] This

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study was approved by the Mayo Clinic and Olmsted Medical Center Institutional Review Boards.

This population-based cohort study of patients with ASCVD consisted of patients with a diagnosis of myocardial infarction (MI), unstable angina (UA), coronary revascularization procedure, or ischemic stroke or transient ischemic attack (TIA) between 2005 and 2012. For each diagnosis, all incident (first-ever) events in Olmsted County residents between January 1, 2005 and December 31, 2012 were identified. The index ASCVD event was defined as the earliest incident event during the time frame. If multiple events occurred on the same day, a hierarchy was used to define the type of index event as ischemic stroke or TIA > MI > UA > coronary revascularization. By design, cohort members could have a previous diagnosis of a different type of CVD before the study period, but the index event was required to be the first-ever diagnosis of that type of CVD. The list of diagnostic codes and rules to define the index events are included in Supplemental Table 1.

Outpatient prescription data and LDL-C measurements were obtained from Mayo Clinic and Olmsted Medical Center. Electronic prescriptions from both institutions were retrieved and converted into RxNorm codes[11] and all outpatient prescriptions for statins (atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin) were obtained. For each statin prescription, the strength, dose, and frequency information were used to calculate an average daily potency. In the event of missing data that precluded the calculation of daily potency, the medical records were manually reviewed to determine the correct daily potency. Likewise, records were manually reviewed when 2 prescriptions were written on the same day but for different statins or different potency. For each statin, the potency cut-offs used to define low-, moderate-, and high-intensity statins are provided in Supplemental Table 2.[12]

Select co-morbidities were ascertained using the Centers for Medicare and Medicaid Chronic Conditions Data Warehouse algorithms,[13] with one exception: for all conditions, we used a 5-year reference period. Thus, patients were considered to have co-morbidity if they met the criteria at any time within the 5 years before their index date. For prior MI, UA, and ischemic stroke or TIA, the same definitions used to identify the cohort were employed, using the 5 years before index as the reference period. For previous coronary revascularization, we did not restrict to the 5 years before index and all previous history was used.

All subsequent CV events, including both incident events (different CV events than the index event) and recurrent events (of the same type as the index event) were obtained through September 30, 2015. Follow-up to ascertain events began the day after hospital discharge for patients hospitalized at index and at day 8 for patients who were not hospitalized at index. The rules for beginning follow-up were chosen to avoid erroneously counting recurrent events due to repeated codes related to the index event. Incident events were defined using the same algorithms to define the cohort (as described in Supplemental Table 1). For recurrent ischemic stroke or TIA, the event had to be the principal reason for a hospitalization. For recurrent MI or UA, the patient was required to be hospitalized, and for those where the diagnosis of MI or UA was not the principal reason for a hospitalization, the medical records were manually reviewed to validate the events. When more than one of an MI, UA, or coronary revascularization occurred during the same hospitalization, this was only counted as one event using the following hierarchy: MI > UA > revascularization. However, if a stroke or TIA occurred during the same hospitalization as an MI, UA, or revascularization, the patient was considered to have experienced 2 CV events. In addition to CV events, all-cause deaths were obtained through September 30, 2015 from death certificates from the State of Minnesota, medical records, and obituaries and notices of death in the local newspapers.

Analyses were performed using SAS/STAT software, version 9.4 (SAS Institute Inc., Cary, North Carolina). The last LDL-C value within 90 days of index was used to categorize patients according to baseline LDL-C. Patient characteristics across categories of baseline LDL-C (<70, 70 to <100, and ≥100 mg/dl) were compared using chi-square tests for categorical variables and ANOVA for continuous variables. Follow-up started at day 90 and continued until date of death, last follow-up, or September 30, 2015, whichever occurred first. Patients with <90 days of follow-up were excluded from the analysis. All values of LDL-C over follow-up were obtained, and LDL-C was treated as a time-dependent variable. Rates of all outcomes (CV events, deaths, and the composite end point of CV event or death) were calculated counting multiple events per person and assigned to LDL-C categories in a time-dependent fashion. Cox proportional hazards regression, modeling time to first event, was used to estimate hazard ratios (HRs) for each outcome after adjusting for age, sex, and previous diagnoses of ASCVD, diabetes, hypertension, heart failure, and chronic kidney disease, which were the only co-morbidities that differed meaningfully in prevalence across baseline value of LDL-C. The proportional hazards assumption of the Cox model was tested by using scaled Schoenfeld residuals and was found to be valid.

Results

Among all subjects with ASCVD between 2005 and 2012 (n = 3,717), those prescribed a moderate-intensity or high-intensity statin and who had at least 1 LDL-C measurement within the first 90 days after index (n = 1,854) were retained. Among these 1,854 patients (mean [SD] age 66.0 [13.3] years, 63.6% male), 778 (42.0%) had MI as their index ASCVD event, 391 (21.1%) had UA, 283 (15.3%) had coronary revascularization, and 402 (21.7%) had ischemic stroke or TIA. Within 90 days after index, the first qualifying LDL-C was <70, 70-<100, and ≥100 mg/dl in 743 (40.1%), 644 (34.7%), and 467 (25.2%) patients, respectively. Patients with lower levels of LDL-C were more likely to be male, and had higher prevalences of diabetes, heart failure, and chronic kidney disease compared with those with higher LDL-C at baseline (Table 1).

Over a median follow-up of 5.9 years, a total of 1,241 events (CV event or all-cause death) were observed from the date of index ASCVD through follow-up. Multiple events per person were captured; 520 patients experienced 1 event and 269 patients experienced 2 or more events over

Table 1
Participant characteristics at index by baseline low-density lipoprotein cholesterol category

Variable	Low-density lipoprotein cholesterol (mg/dl)				p Value
	Overall (n = 1,854)	<70 (n = 743)	70 to <100 (n = 644)	≥100 (n = 467)	
Age (years)	66.0 (13.3)	66.4 (13.2)	66.6 (13.2)	64.5 (13.6)	0.026
Men	1,179 (63.6%)	504 (67.8%)	416 (64.6%)	259 (55.5%)	<0.001
Ever smoker	1,266 (68.8%)	505 (68.2%)	433 (67.9%)	328 (71.0%)	0.496
Body mass index (kg/m2)					0.349
<25	395 (21.9%)	168 (23.0%)	124 (19.9%)	103 (23.0%)	
25 to <30	704 (39.1%)	267 (36.5%)	262 (42.1%)	175 (39.2%)	
≥30	702 (39.0%)	297 (40.6%)	236 (37.9%)	169 (37.8%)	
Prior ASCVD	274 (14.8%)	135 (18.2%)	96 (14.9%)	32 (9.2%)	0.001
Prior myocardial infarction	141 (7.6%)	80 (10.8%)	44 (6.8%)	17 (3.6%)	<0.001
Prior unstable angina	48 (2.6%)	26 (3.5%)	15 (2.3%)	7 (1.5%)	0.090
Prior coronary revascularization	171 (9.2%)	78 (10.5%)	63 (9.8%)	30 (6.4%)	0.049
Prior stroke/transient ischemic attack	14 (0.8%)	7 (0.9%)	7 (1.1%)	0	0.044
Prior hypertension	1,181 (63.7%)	489 (65.8%)	416 (64.6%)	276 (59.1%)	0.052
Prior diabetes mellitus	446 (24.1%)	218 (29.3%)	150 (23.3%)	78 (16.7%)	<0.001
Prior heart failure	222 (12.0%)	106 (14.3%)	82 (12.7%)	34 (7.3%)	0.001
Prior chronic obstructive pulmonary disease	222 (12.0%)	79 (10.6%)	81 (12.6%)	62 (13.3%)	0.326
Prior chronic kidney disease	254 (13.7%)	125 (16.8%)	88 (13.7%)	41 (8.8%)	<0.001

ASCVD, atherosclerotic cardiovascular disease.
Values are presented as N (%) for categorical variables and mean (SD) for continuous variables.

follow-up. The rate (95% confidence interval [CI]) per 100 person-years of the composite outcome of CV event or death was 11.26 (10.64 to 11.91), which included 153 events that occurred between index date and LDL-C measurement (Table 2).

The median number of LDL-C measurements over follow-up was 5 (range of 1 to 35), and 820 (44.2%) patients remained in the same LDL-C category over their follow-up. Accounting for changes in LDL-C over time and beginning follow-up 90 days after index ASCVD, the rates (95% CI) per 100 person-years of the composite outcome (CV event or all-cause death) were 10.51 (9.57 to 11.52), 9.57 (8.66 to 10.55), and 11.40 (9.96 to 12.98) for LDL-C <70, 70-<100, and ≥100 mg/dl, respectively (Table 3). After adjustment for age, sex, and previous diagnoses of ASCVD, diabetes, hypertension, heart failure, and chronic kidney disease, the HRs for the composite outcome (HR 1.31, 95% CI 1.08 to 1.59) and all-cause death (HR 1.64, 95% CI 1.26 to 2.12) were significantly higher for patients with LDL-C ≥100 versus <70 mg/dl, whereas no difference was observed across LDL-C categories for CV events (p = 0.78; Figure 1).

Table 2
Overall counts and rates of cardiovascular events and all-cause deaths in patients with atherosclerotic cardiovascular disease

	All patients (n = 1,854)
Composite outcome (CV events + death)	
Number of events	1,241
Number of patients with 1 event	520
Number of patients with ≥2 events	269
Total person-years of follow-up	11,019.85
Rate (95% CI) per 100 person-years	11.26 (10.64−11.91)
Cardiovascular events	
Number of events	857
Number of patients with 1 event	376
Number of patients with ≥2 events	176
Total person-years of follow-up	11,019.85
Rate (95% CI) per 100 person-years	7.78 (7.26−8.32)
All-cause death	
Number of events	384
Total person-years of follow-up	11,019.85
Rate (95% CI) per 100 person-years	3.48 (3.14-3.85)

CI, confidence interval; CV, cardiovascular.
Rates are calculated counting multiple events per person. Follow-up began at the date of index atherosclerotic cardiovascular disease.

Discussion

In this population-based cohort study of 1,854 patients with ASCVD who were prescribed moderate- or high-intensity statins, a large number of CV events and deaths were observed over a median follow-up of 5.9 years, with a composite rate (including multiple events per person) of 11.26 per 100 person-years. This overall event rate is comparable to previous published estimates in other nonrandomized controlled trial (RCT) settings.[14]

The UK-based Clinical Practice Research Datalink, a cohort at high risk for ASCVD that was relatively comparable to this US-based cohort with mean age of 67, 60% male, and a high prevalence of hypertension and diabetes, had a multiple-event composite CV event rate of 12.3 per 100 person-years.[14] A review of the global real-world CVD burden in patients with previous major adverse CV events and elevated LDL-C found similarly that 2 additional studies reported multiple event rates ranging from 6.0 to 39.1 events per 100 person-years.[15]

The observed event rate of 11.26 per 100 person-years in this observational study is much higher than that found in RCTs. The Cholesterol Treatment Trialists' Collaboration meta-analysis published in 2010 reported composite CV event rates ranging from 2.8 to 5.3 per 100 person-years.[2]

Table 3
Counts and rates of cardiovascular events and all-cause deaths across categories of low-density lipoprotein cholesterol

	Low-density lipoprotein cholesterol category			
	<70 mg/dl	70 to <100 mg/dl	≥100 mg/dl	p Value
Composite outcome (CV events + death)				
Number of events	455	406	227	
Total person-years of follow-up	4,328.75	4,242.94	1,991.32	
Rate (95% CI) per 100 person-years	10.51 (9.57−11.52)	9.57 (8.66−10.55)	11.40 (9.96−12.98)	0.095
Cardiovascular events				
Number of events	304	268	132	
Total person-years of follow-up	4328.75	4242.94	1991.32	
Rate (95% CI) per 100 person-years	7.02 (6.26−7.86)	6.32 (5.58−7.12)	6.63 (5.55−7.86)	0.447
All-cause death				
Number of events	151	138	95	
Total person-years of follow-up	4,328.75	4,242.94	1,991.32	
Rate (95% CI) per 100 person-years	3.49 (2.95−4.09)	3.25 (2.73−3.84)	4.77 (3.86−5.83)	0.015

CI, confidence interval; CV, cardiovascular.

Rates are calculated counting multiple events per person and assigned to low-density lipoprotein categories in a time-dependent fashion. Follow-up began 90 days after the date of index atherosclerotic cardiovascular disease.

This difference supports a growing impression that, while RCTs are considered the gold standard for establishing efficacy of specific interventions, the RCT design with its tightly-controlled inclusion and exclusion criteria, close monitoring of patients, and capture of first events only, may not be as valid when describing the real-world disease burden.[16]

To our knowledge, there are no publications examining CV event rates by categories of LDL-C, likely due to the lack of LDL-C values, particularly over time, in most claims databases. However, due to the extensive record linkages available in the REP, this study was able to examine LDL-C values in a time-dependent manner in relation to CV events using all available measurements (up to 35 per patient; median = 5). At baseline (within 90 days after index ASCVD event), 60% of the patients were not at LDL-C goal per the guidelines in practice during the study period (National Cholesterol Education Program Adult Treatment Panel III guidelines stated that patients with ASCVD should have LDL <70 mg/dl).[17] Further, 25% had LDL-C >100 mg/dl which is in line with previous estimates of the proportion of treated hyperlipidemia patients who continue to have elevated LDL-C.[18]

The high proportions of patients with LDL-C >70 mg/dl and especially >100 mg/dl are notable in that all patients in this study were already being treated with moderate- to high-intensity statins. Coupled with the observation that event rates were high across all 3 groups of LDL-C (although increased risks of death and the composite outcome in those with LDL-C ≥100 mg/dl was observed), these results indicate that there are large unmet treatment needs even among patients receiving moderate- to high-intensity statins. Current American Heart Association/American College of Cardiology guidelines recommend

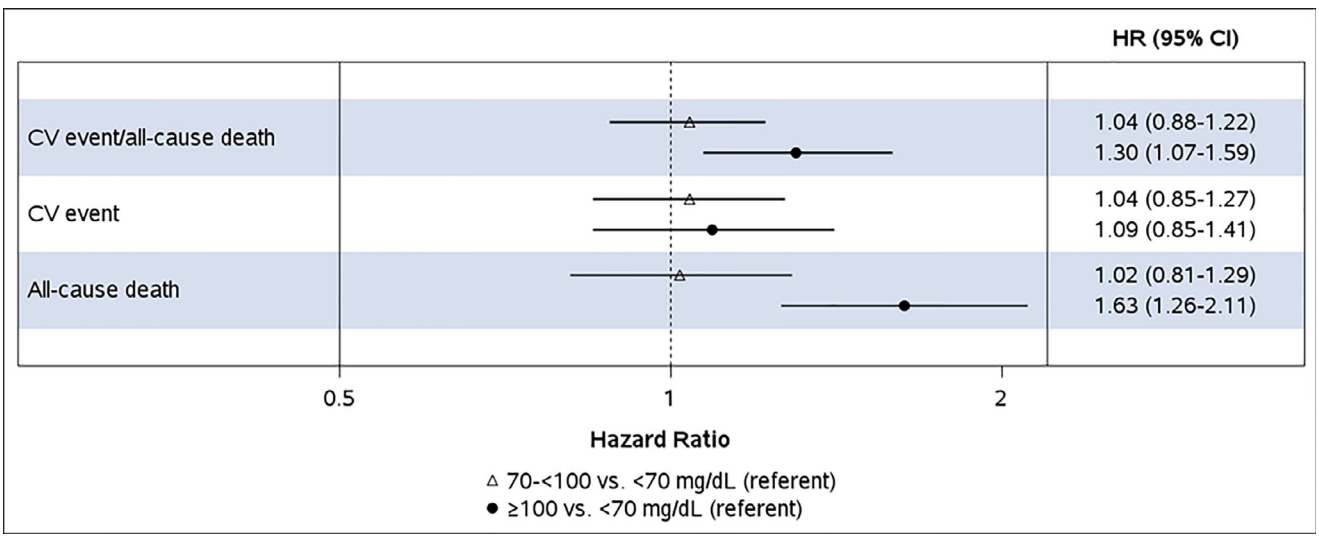

Figure 1. Hazard ratios (95% confidence interval) for cardiovascular events and all-cause death according to low-density lipoprotein cholesterol category. Hazard ratios are calculated modeling low-density lipoprotein cholesterol as a time-dependent variable and adjusting for age, sex, previous atherosclerotic cardiovascular disease, previous diabetes, previous hypertension, previous heart failure, and previous chronic kidney disease. CV, cardiovascular.

high-intensity statin use (or moderate-intensity in those aged ≥75 years) for patients with ASCVD.[12] However, our results indicate that more aggressive or alternative treatment may be necessary to reduce the burden of subsequent CV events in patients at high-risk after an initial ASCVD event.

In the patients for whom LDL-C was <70 mg/dl, the composite event rate and death rate were significantly lower than patients with LDL-C ≥100 mg/dl. However, a clear graded association was not observed and the risk of CV events was not different across the LDL-C categories. It is unclear why our observation is in contrast with evidence from clinical trials that have indicated lower CV event rates in relation to lowering of LDL-C.[2,5,6] Although we cannot rule out the possibility that patients in our study with LDL-C <70 mg/dl have a higher co-morbidity burden that could not be adjusted for due to unmeasured confounders, these patients with the lowest LDL-C levels continued to experience CV events at a high rate. Additional research is warranted to determine whether similar CV event rates are observed for those with LDL-C <70 mg/dl compared with patients whose LDL-C levels are not as well controlled in larger and more diverse populations. Nevertheless, the findings of our study call to question whether clinicians should limit the oft-held assumption that well-controlled LDL-C values (<70 mg/dl) are adequate to reduce the CV event rate.

Some limitations deserve mention. The cohort was relatively small and thus results should be interpreted within this context. These results may serve to generate hypotheses to be tested in future studies, and should be replicated in larger and more diverse populations. Although the Olmsted County population is representative of the state of Minnesota and the Upper Midwest region of the US,[8] the results may not be generalizable to the entire US or other populations worldwide. In addition, we included only ASCVD patients treated with a moderate- or high-intensity statin in our analyses; thus, it is unknown whether similar associations would be observed in ASCVD patients treated with low-intensity statins, nonstatin therapy, or no lipid-lowering therapy. Finally, residual confounding of the estimates may exist and may have affected the results due to the inability to adjust for unmeasured confounders.

This study has several unique strengths. The data represent the experience of a community with outcomes captured in a "real world" setting as opposed to a clinical trial setting. As such, the long follow-up allowed for the inclusion of repeated measures of LDL-C over time as well as the capture of all outcomes, including multiple events per person. Furthermore, the rigorous data collection methods employed, including manual record review, allowed the capture of both incident and recurrent CV events, garnering important data of clinical relevance.

In patients with ASCVD treated with moderate- to high-intensity statins, although LDL-C levels are well-controlled in some patients, a large proportion of patients had LDL-C >70 mg/dl despite appropriate statin treatment. In this population-based cohort, subsequent CV events occurred at a high rate in all patients. The risk of the composite end point and of death were highest for patients with LDL-C ≥100 mg/dl, although no differences in CV events were observed across levels of LDL-C. This finding suggests that there may be unmet treatment needs in patients receiving moderate- to high-intensity statins; additional work is needed to examine this question in larger studies and diverse populations.

Author Agreement

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Supplementary materials

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