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Association Between Achieved Low-Density Lipoprotein Levels and Major Adverse Cardiac Events in Patients With Stable Ischemic Heart Disease Taking Statin Treatment

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IMPORTANCE International guidelines recommend treatment with statins for patients with preexisting ischemic heart disease to prevent additional cardiovascular events but differ regarding target levels of low-density lipoprotein cholesterol (LDL-C). Trial data on this question are inconclusive and observational data are lacking.

OBJECTIVE To assess the relationship between levels of LDL-C achieved with statin treatment and cardiovascular events in adherent patients with preexisting ischemic heart disease.

DESIGN, SETTING, AND PARTICIPANTS Population-based observational cohort study from 2009 to 2013 using data from a health care organization in Israel covering more than 4.3 million members. Included patients had ischemic heart disease, were aged 30 to 84 years, were treated with statins, and were at least 80% adherent to treatment or, in a sensitivity analysis, at least 50% adherent. Patients with active cancer or metabolic abnormalities were excluded.

EXPOSURES Index LDL-C was defined as the first achieved serum LDL-C measure after at least 1 year of statin treatment, grouped as low (≤70.0 mg/dL), moderate (70.1-100.0 mg/dL), or high (100.1-130.0 mg/dL).

MAIN OUTCOMES AND MEASURES Major adverse cardiac events included acute myocardial infarction, unstable angina, stroke, angioplasty, bypass surgery, or all-cause mortality. The hazard ratio of adverse outcomes was estimated using 2 Cox proportional hazards models with low vs moderate and moderate vs high LDL-C, adjusted for confounders and further tested using propensity score matching analysis.

RESULTS The cohort with at least 80% adherence included 31 619 patients, for whom the mean (SD) age was 67.3 (9.8) years. Of this population, 27% were female and 29% had low, 53% moderate, and 18% high LDL-C when taking statin treatment. Overall, there were 9035 patients who had an adverse outcome during a mean 1.6 years of follow-up (6.7 per 1000 persons per year). The adjusted incidence of adverse outcomes was not different between low and moderate LDL-C (hazard ratio [HR], 1.02; 95% CI, 0.97-1.07; $P = .54$), but it was lower with moderate vs high LDL-C (HR, 0.89; 95% CI, 0.84-0.94; $P < .001$). Among 54 884 patients with at least 50% statin adherence, the adjusted HR was 1.06 (95% CI, 1.02-1.10; $P = .001$) in the low vs moderate groups and 0.87 (95% CI, 0.84-0.91; $P = .001$) in the moderate vs high groups.

CONCLUSIONS AND RELEVANCE Patients with LDL-C levels of 70 to 100 mg/dL taking statins had lower risk of adverse cardiac outcomes compared with those with LDL-C levels between 100 and 130 mg/dL, but no additional benefit was gained by achieving LDL-C of 70 mg/dL or less. These population-based data do not support treatment guidelines recommending very low target LDL-C levels for all patients with preexisting heart disease.

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Patients with stable ischemic heart disease (IHD) are at increased risk for recurrent cardiovascular events, and clinical practice guidelines recommend long-term treatment with statins. There are, however, differences among current guidelines regarding the definition of appropriate targets for low-density lipoprotein cholesterol (LDL-C) levels. The American Heart Association's guidelines define treatment by medication intensity and do not establish target LDL-C levels,[1] whereas the European Society of Cardiology recommends that treatment be titrated to achieve an LDL-C level below 70 mg/dL (to convert milligrams per deciliter to millimoles per liter, multiply by 0.0259).[2]

The major study cited in guidelines as evidence for achieving low LDL-C levels is a meta-analysis of randomized clinical trials (RCTs) demonstrating a reduction in cardiovascular events with more intensive statin therapy.[3] Two of these landmark RCTs demonstrated significantly improved clinical outcomes with more intensive compared with less intensive statin therapy.[4,5] Subsequent post hoc analyses of these 2 RCTs examined achieved LDL-C levels and clinical outcomes, and reported nonsignificant findings of improved efficacy at lower LDL-C levels.[6,7]

Results from recent clinical trials of statins in combination with adjunctive medications for secondary prevention[8-10] have led to renewed emphasis on the concept that "lower is better" for target LDL-C levels.[11] The question of the association between achieved LDL-C levels and major adverse cardiac events (MACEs) for secondary prevention has become highly relevant, particularly in the real-world context of patients excluded from RCTs. The present population-based observational study examines whether the principle of lower is better is applicable to long-term treatment of patients with IHD in the community setting, by assessing the relationship between observed LDL-C levels and cardiovascular outcomes in the largest health care organization in Israel.

Key Points

Question Should a clinician treating a patient with chronic ischemic heart disease who is already taking statins make changes to treatment regimens to lower low-density lipoprotein cholesterol (LDL-C) level below 70 mg/dL?

Findings This cohort study of 31 619 patients showed no decrease in cardiac events from lowering LDL-C level below 70 mg/dL compared with patients with LDL-C between 70 and 100 mg/dL.

Meaning Our data do not support recommendations that treating to LDL-C levels below 70 mg/dL are relevant for all patients with ischemic heart disease, particularly those who are adherent to statin treatment.

Methods

Study Design

This observational cohort study compares risk of MACEs among IHD patient subgroups by observed LDL-C levels after at least 1 year of statin therapy.

Data Source

Data for all Clalit Health Services (CHS) members were collected for this study from CHS's comprehensive clinical and administrative data warehouse. Anonymous patient data were compiled from electronic medical records, the organization's chronic disease registry, hospital discharge summaries, and pharmacy and laboratory records. Patients' demographic data were collected from the Israeli Central Bureau of Statistics and the Ministry of Internal Affairs. The CHS institutional review board waived the requirement for patient consent because of the retrospective nature of the study and approved this study.

Study Cohort

The cohort included patients aged 30 to 84 years with preexisting IHD, defined as a previous acute diagnosis requiring secondary prevention including myocardial infarction, unstable angina, percutaneous transluminal coronary angioplasty (PTCA), or coronary artery bypass grafting before the index date. Cohort entry was the date of the first serum LDL-C value any time from January 1, 2009, to December 31, 2013, that was preceded by at least 1 year of adherence to statin therapy. Adherence to statin therapy was derived from a prescription-based medication possession ratio and was defined as fulfillment of at least 80% of statin prescriptions. The prescription-based medication possession ratio is the proportion of days covered by dispensed medication during a period from the first to the last written prescription during the preindex year—a methodology validated for measuring statin adherence.[12] Adherence of at least 80% was used to allow for the effect of statin use.

Patients were excluded if they manifested uncontrolled metabolic abnormalities, including a fasting glucose test value of 300 mg/dL or higher, a serum thyrotropin level above 6 mIU/L or below 0.4 mIU/L, LDL-C level greater than 130 mg/dL, or a triglyceride test result of 600 mg/dL or higher in the 3 months preceding the index date. Patients with active cancer (receiving antineoplastic treatment during the preindex year) were also excluded. Patients who were not continuous members during the preindex year were excluded. **Figure 1** illustrates the patient exclusions diagram.

Variables

The exposure was the first observed LDL-C level achieved after at least 1 year of statin use, which was categorized on the basis of levels indicated in established guidelines[2] as low (≤70.0 mg/dL), moderate (70.1-100.0 mg/dL), or high (100.1-130.0 mg/dL).

Covariates adjusted for in Cox regression models and sensitivity analyses were baseline characteristics measured during the preindex year. These included population sector and socioeconomic status data that were based on the aggregate classification of the patient's primary care clinic.[13] Socioeconomic status was classified as low or mid-high, and the population sector was classified as Jewish or non-Jewish. Patient clinical variables included preindex body mass index and time taking statins (≥12 months). Statin treatment regimens were assessed as low (equivalent to simvastatin ≤20 mg), moderate (equivalent to simvastatin 40 mg), and high (equivalent to

simvastatin 80 mg) potency, based on the US Food and Drug Administration's classification (eTable 1 in the Supplement).[14] The Charlson comorbidity index[15] (categorized as scores of 0-1, 2, 3-4, and ≥5) was used to indicate morbidity burden. Chronic kidney disease (CKD) was classified on the basis of the calculated estimated glomerular filtration rate[16] of the last serum creatinine test performed before the index date. The number of concomitant long-term medications was measured at the index date, grouped as 0 to 4, 5 to 7, or 8 or more drugs, and insulin use was noted. Health service use was defined according to event counts during 2 years prior to the index date and included number of physician visits, PTCAs, and lipid profiles, each categorized at levels suggesting clinical instability. eTable 4 in the Supplement shows which covariates were included in the various models in the analyses.

The study outcome was the first occurrence of MACE, which included any of the following collected from the hospital discharge records of the CHS data warehouse (*International Classification of Diseases, Ninth Revision,* codes detailed in eTable 2 in the Supplement): myocardial infarction, unstable angina, stroke, percutaneous coronary intervention, coronary artery bypass grafting, or all-cause mortality during the study period.

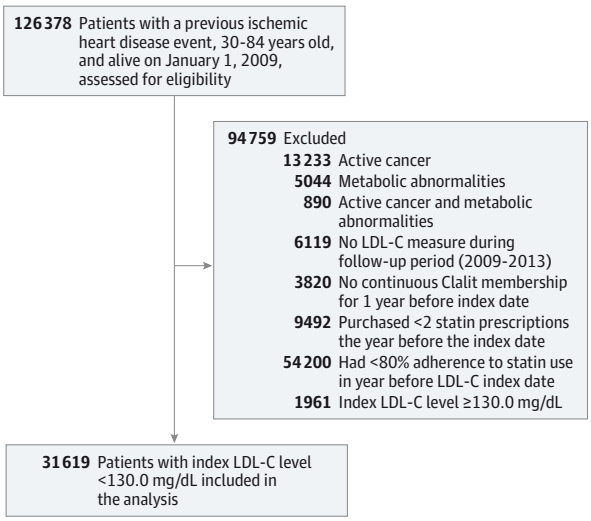
Statistical Analysis

We examined the distribution of sociodemographic and clinical characteristics comparing the low and moderate LDL-C groups, and the moderate and high LDL-C groups, using χ^2, *t* tests, and Mann-Whitney to test for differences. Kaplan-Meier survival analysis assessed differences in time to MACE by index LDL-C groups using the log rank test (eFigure 1 in the Supplement).

Cox proportional hazard analyses were conducted as 2 separate models to determine the hazard for MACE by achieved LDL-C group: (1) low vs moderate and (2) moderate vs high. Patients with no event were censored on December 31, 2013. Forward stepwise regression was used, and the LDL-C group was forced into all models. We repeated all analyses stratified by age according to patients older or younger than 75 years to see whether there was a differential association by age, as observed in a previous study.[8]

To further confirm the association of MACEs and LDL-C level, we conducted a secondary analysis using propensity score (PS) matching because the 3 LDL-C groups differed significantly across baseline characteristics. Propensity score analyses were also conducted as 2 models with separate propensity scores for low vs moderate and moderate vs high LDL-C groups. Further details on the PS analysis and matching methods can be found in eTables 4 through 6 and eFigures 2 and 3 in the Supplement. When analyzing the PS-matched population, a robust variance sandwich-type method was used to account for pairing.[17] Additionally, we performed several sensitivity analyses. In the first, we assessed MACE outcomes excluding all-cause mortality because cause-specific mortality data were not available. Second, we used a restricted cubic spline analysis with knots at LDL-C levels of 70.0 and 100.0 mg/dL to examine the association with LDL-C as a continuous exposure.[18] Last, we evaluated patients with IHD who were at least 50% adherent to their statin medication to represent a more common clinical scenario (rather than ≥80% adherence). Based on the population size, we estimated 90% power to detect an 8% reduction in hazard for MACEs between the groups. Analyses were performed using SPSS, version 22.0.0.1, and R (R Foundation for Statistical Computing), version 3.1.1, with Matching (version 4.8-3.4) and Coxphw (version 3.0.0) packages.[19]

Figure 1. Study Population Exclusions Diagram



LDL-C indicates low-density lipoprotein cholesterol.

Results

In January 2009, there were 126 378 adult CHS members between the ages of 30 and 84 years with IHD. After all exclusions were applied, the final study population comprised 31 619 patients with IHD who were at least 80% adherent to their statin treatment prior to their index LDL-C measurement (Figure 1). There were 9086 (29%) patients who had an index LDL-C of 70.0 mg/dL or less, 16 782 (53%) patients with an index LDL-C between 70.1 and 100.0 mg/dL, and 5751 (18%) patients with an index LDL-C between 100.1 and 130.0 mg/dL (**Table 1**). Overall, 9035 patients had a MACE or died during a mean 1.6 years of follow-up (incidence rate, 6.7 per 1000 persons per year).

The mean (SD) age in the low and moderate LDL-C groups was 67.8 (9.6) and 67.4 (9.7) ($P < .001$), with 23.7% and 27.4% female, respectively ($P < .001$) (Table 1). Compared with the moderate LDL-C group, the patients with low LDL-C had significantly more comorbidities, such as diabetes (62.5% vs 52.0%; $P < .001$), congestive heart failure (18.7% vs 15.4%; $P < .001$), and severe CKD (stages 4 and 5) (4.4% vs 3.2%; $P < .001$) and more were taking multiple long-term medications (≥8 medications) (73.2% vs 65.2%; $P < .001$). The low LDL-C group had 29.5% MACEs compared with 27.4% in the moderate LDL-C group ($P < .001$) (Table 1).

In the high LDL-C group, the mean (SD) age was 66.4 (10.3) years, and there were 32.4% women (Table 1). There was a

Table 1. Patient Characteristics for Low-Density Lipoprotein Cholesterol (LDL-C) Groups

Characteristic	LDL-C Group[a]			*P* Value	
	Low (n = 9086)	Moderate (n = 16 782)	High (n = 5751)	Low vs Moderate	Moderate vs High
Age					
Mean (SD), y	67.8 (9.6)	67.4 (9.7)	66.4 (10.3)	<.001	<.001
Median (IQR), y	69.0 (61.0-76.0)	68.0 (60.0-75.0)	67.0 (59.0-75.0)	<.001	<.001
No. (%)					
30-49 y	317 (3.5)	607 (3.6)	308 (5.4)	<.001	<.001
50-64 y	3048 (33.5)	6052 (36.1)	2251 (39.1)		
65-74 y	3136 (34.5)	5509 (32.8)	1715 (29.8)		
75-84 y	2585 (28.5)	4614 (27.5)	1477 (25.7)		
Sex, No. (%)					
Male	6931 (76.3)	12180 (72.6)	3890 (67.6)	<.001	<.001
Female	2155 (23.7)	4602 (27.4)	1861 (32.4)		
Ethnicity, No. (%)					
Jewish	8220 (90.5)	15224 (90.7)	4976 (86.5)	.53	<.001
Non-Jewish	866 (9.5)	1558 (9.3)	775 (13.5)		
Socioeconomic status, No. (%)					
Mid-high	6172 (67.9)	11548 (68.8)	3689 (64.1)	.15	<.001
Low	2914 (32.1)	5234 (31.2)	2062 (35.9)		
Index LDL-C level, mg/dL					
Mean (SD)	58.4 (9.8)	84.0 (8.3)	111.2 (7.9)	<.001	<.001
Median (IQR)	60.7 (53.5-65.9)	83.6 (77.0-91.0)	109.8 (104.4-117.0)	<.001	<.001
HDL-C level, mg/dL					
Mean (SD)	45.0 (11.9)	47.7 (11.7)	48.9 (12.5)	<.001	<.001
Median (IQR)	43.0 (37.0-51.0)	46.0 (39.0-54.0)	47.0 (40.0-55.0)	<.001	<.001
BMI					
Mean (SD)	29.2 (5.1)	29.0 (5.1)	29.3 (5.3)	.002	<.001
Median (IQR)	28.4 (25.7-31.6)	28.2 (25.6-31.4)	28.6 (25.8-31.9)	.002	<.001
No. (%)					
<18.5	4059 (44.7)	7553 (45.0)	9 (0.2)	.08	<.001
18.5-24.9	14 (0.2)	37 (0.2)	1061 (18.4)		
25.0-29.9	1671 (18.4)	3205 (19.1)	2438 (42.4)		
≥30.0	3225 (35.5)	5731 (34.1)	2156 (37.5)		
Unknown	117 (1.3)	256 (1.5)	87 (1.5)		
Chronic conditions, No. (%)					
Diabetes	5676 (62.5)	8732 (52.0)	2863 (49.8)	<.001	.003
Insulin use	731 (8.0)	917 (5.5)	297 (5.2)	<.001	.40
Hypertension	4104 (45.2)	7275 (43.4)	2461 (42.8)	.005	.47
Congestive heart failure	1701 (18.7)	2578 (15.4)	898 (15.6)	<.001	.66
Atrial fibrillation	1230 (13.5)	1900 (11.3)	646 (11.2)	<.001	.87
Cerebrovascular accident	62 (0.7)	89 (0.5)	45 (0.8)	.15	.04
Charlson score, No. (%)					
0-1	5409 (59.5)	8660 (51.6)	373 (6.5)	<.001	<.001
2	334 (3.7)	838 (5.0)	661 (11.5)		
3-4	744 (8.2)	1846 (11.0)	1786 (31.1)		
≥5	2525 (27.8)	5354 (31.9)	2902 (50.5)		
Unknown	74 (0.8)	84 (0.5)	29 (0.5)		

(continued)

Table 1. Patient Characteristics for Low-Density Lipoprotein Cholesterol (LDL-C) Groups (continued)

Characteristic	LDL-C Group[a]			*P* Value	
	Low (n = 9086)	Moderate (n = 16 782)	High (n = 5751)	Low vs Moderate	Moderate vs High
Chronic kidney disease stage, No. (%)					
1	1815 (20.0)	3764 (22.4)	1381 (24.0)	<.001	.003
2	4438 (48.8)	8597 (51.2)	2782 (48.4)		
3A	1445 (15.9)	2360 (14.1)	807 (14.0)		
3B	785 (8.6)	1132 (6.7)	414 (7.2)		
4	292 (3.2)	442 (2.6)	165 (2.9)		
5	107 (1.2)	104 (0.6)	38 (0.7)		
Unknown	204 (2.2)	383 (2.3)	164 (2.9)		
PTCA, No. (%)					
0	7779 (85.6)	14791 (88.1)	5100 (88.7)	<.001	.26
1-2	1247 (13.7)	1924 (11.4)	623 (10.8)		
≥3	60 (0.7)	67 (0.4)	28 (0.5)		
>24 Visits, No. (%)	5619 (61.8)	9382 (55.9)	3073 (53.4)	<.001	.001
>9 Lipid profiles, No. (%)	4558 (50.2)	7607 (45.3)	2443 (42.5)	<.001	<.001
No. of long-term medications, No. (%)					
0-4	552 (6.1)	1587 (9.5)	615 (10.7)	<.001	.003
5-7	1879 (20.7)	4250 (25.3)	1511 (26.3)		
≥8	6655 (73.2)	10 945 (65.2)	3625 (63.0)		
Time taking statins, y					
Mean (SD)	6.6 (3.4)	7.3 (3.2)	7.6 (3.1)	<.001	<.001
Median (IQR)	7.0 (4.0-10.0)	8.0 (5.0-10.0)	8.0 (5.0-11.0)	<.001	<.001
Statin potency, No. (%)					
Low	447 (4.9)	967 (5.8)	505 (8.8)	.004	<.001
Medium	4764 (52.4)	8483 (50.5)	2749 (47.8)		
High	3846 (42.3)	7276 (43.4)	2460 (42.8)		
Missing	29 (0.3)	56 (0.3)	37 (0.6)		
Statin used, No. (%)					
Simvastatin	4870 (53.6)	8423 (50.2)	2742 (47.7)	<.001	.001
Atorvastatin	2472 (27.2)	5487 (32.7)	2000 (34.8)	<.001	.004
Rosuvastatin	1606 (17.7)	2351 (14.0)	668 (11.6)	<.001	<.001
Pravastatin	138 (1.5)	520 (3.1)	340 (5.9)	<.001	<.001
MACEs[a]	2681 (29.5)	4595 (27.4)	1759 (30.6)	<.001	<.001

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiac event; PTCA, percutaneous transluminal coronary angioplasty.

SI conversion factor: To convert milligrams per deciliter to millimoles per liter, multiply by 0.0259.

[a] Index LDL-C was grouped as low (≤70.0 mg/dL), moderate (70.1-100.0 mg/dL), or high (100.1-130.0 mg/dL).

[b] Outcome.

higher rate of diabetes in the moderate LDL-C group than the high LDL-C group (52.0% vs 49.8%; *P* = .003) but slightly lower rates of severe CKD (stages 4 and 5) (3.2% vs 3.6%; *P* = .003) and cerebrovascular accident (0.5% vs 0.8%; *P* = .04) compared with the high LDL-C group. There were no other statistically significant differences in comorbidities between the 2 groups. More patients in the moderate LDL-C group were taking multiple long-term medications (≥8) than in the high LDL-C group (65.2% vs 63.0%; *P* = .003), but there was a lower rate of MACE (27.4% vs 30.6%; *P* < .001).

There were 4595 MACEs (71.0 per 1000 person-years) among the moderate LDL-C group and 2681 events (78.1 per 1000 person-years) among the low LDL-C group. The unadjusted hazard ratio (HR) for MACE in these groups was 1.10 (95% CI, 1.05-1.15; *P* < .001), and the adjusted HR was 1.02 (95% CI, 0.97-1.07; *P* = .54) (**Table 2**). Among the high LDL-C group, there were 1759 MACEs (rate of 81.3 per 1000 person-years). The unadjusted HR compared with the moderate group was 0.87 (95% CI, 0.83-0.92; *P* < .001) and the adjusted HR was 0.89 (95% CI, 0.84-0.94; *P* < .001). The number of events for each component of MACE by LDL-C group can be found in eTable 3 in the Supplement.

When stratified by age, the adjusted HR for the low vs moderate LDL-C groups was not significantly different: 1.00 (95% CI, 0.94-1.06; *P* = .89) and 1.05 (95% CI, 0.97-1.14; *P* = .26) for patients younger and older than 75 years, respectively (Table 2). In the moderate vs high LDL-C groups, the HR for the adjusted analyses was 0.89 (95% CI, 0.83-0.95; *P* = .001) for patients younger than 75 years and 0.87 (95% CI, 0.79-0.96; *P* = .005) for patients aged at least 75 years.

In the secondary analysis among the PS-matched population, there were 2583 MACEs among the low LDL-C group and

Table 2. Hazard Ratio (HR) of Major Cardiac Events (MACEs) Comparing Achieved Low vs Moderate and Moderate vs High Levels of Low-Density Lipoprotein (LDL-C) Among All Patients, Patients Stratified by Age, and the Propensity-Matched Population

Analysis	LDL-C Group[a]									
	Low		Moderate		High		Low vs Moderate		Moderate vs High	
	Patients, No.	MACEs, No. (Rate per 1000 Person-years)	Patients, No.	MACEs, No. (Rate per 1000 Person-years)	Patients, No.	MACEs, No. (Rate per 1000 Person-years)	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
All Patients										
Unadjusted	9041	2681 (78.1)	16 782	4595 (71.0)	5751	1759 (81.3)	1.10 (1.05-1.15)	<.001	0.87 (0.83-0.92)	<.001
Adjusted[b]	9041	2681 (78.1)	16 782	4595 (71.0)	5751	1759 (81.3)	1.02 (0.97-1.07)	.54	0.89 (0.84-0.94)	<.001
Patients Stratified by Age										
Age <75 y[c]	6464	1708 (68.8)	12 168	3022 (63.8)	4274	1183 (72.4)	1.00 (0.94-1.06)	.89	0.89 (0.83-0.95)	.001
Age ≥75 y[d]	2577	953 (101.7)	4614	1573 (90.7)	1477	576 (108.2)	1.05 (0.97-1.14)	.26	0.87 (0.79-0.96)	.005
Propensity-Matched Population										
Low vs moderate LDL-C										
Unadjusted	8833	2583 (77.2)	8833	2625 (78.3)	...	...	0.99 (0.93-1.04)	.63	...	...
Adjusted[e]	8833	2583 (77.2)	8833	2625 (78.3)	...	...	1.00 (0.94-1.05)	.86	...	...
Moderate vs high LDL-C										
Unadjusted	...	...	5739	1614 (73.3)	5739	1757 (81.4)	...	...	0.90 (0.84-0.96)	.003
Adjusted[e]	...	...	5739	1614 (73.3)	5739	1757 (81.4)	...	...	0.90 (0.84-0.96)	.002

Abbreviations: BMI, body mass index; CKD, chronic kidney disease; ellipses, not applicable.

SI conversion factor: To convert milligrams per deciliter to millimoles per liter, multiply by 0.0259.

[a] Index LDL-C was grouped as low (≤70.0 mg/dL), moderate (70.1-100.0 mg/dL), or high (100.1-130.0 mg/dL).

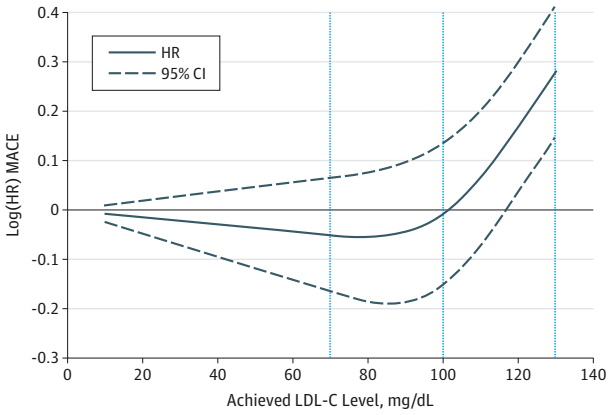
[b] Adjusted for the following variables: age, sex, ethnicity, socioeconomic status, smoking status, diabetes, insulin use, time taking statins, physician visits, CKD stage, number of angioplasties, Charlson risk score, BMI.

[c] Adjusted for the following variables: sex, ethnicity, socioeconomic status, smoking status, diabetes, insulin use, time taking statins, physician visits, CKD stage, number of angioplasties, Charlson risk score, BMI.

[d] Adjusted for the following variables: sex, ethnicity, socioeconomic status, smoking status, diabetes, insulin use, time taking statins, physician visits, CKD stage, number of angioplasties, BMI.

[e] Adjusted for the following variables: age, sex, ethnicity, socioeconomic status, smoking status, diabetes, insulin use, time taking statins, physician visits, CKD stage, number of angioplasties, Charlson risk score, BMI.

Figure 2. Estimated Cubic Spline Transformation of the Association Between Achieved Low-Density Lipoprotein Cholesterol (LDL-C) Level and the Risk of Major Adverse Cardiac Events (MACEs)



Vertical dotted lines separate index LDL-C groups (low, ≤70.0 mg/dL; moderate, 70.1-100.0 mg/dL; high, 100.1-130.0 mg/dL). HR indicates hazard ratio.

2625 events among the moderate LDL-C group, with 8833 patients in each group (Table 2). There were 1757 MACEs among the high LDL-C group and 1614 in the PS-matched moderate LDL-C group (Table 2). These results were consistent with what was found in the unmatched analyses. In the cubic spline analysis, the curve was steeper above and slightly below LDL-C of 100.0 mg/dL and flattened before LDL-C of 70.0 mg/dL (**Figure 2**). In our sensitivity analyses excluding all-cause mortality in the outcomes, results were also consistent with the main analysis (**Table 3**). When assessing the association between LDL-C and MACE among patients at least 50% adherent to statin therapy, the results varied from the main analysis in the moderate vs low LDL-C model with an adjusted HR of 1.06 (95% CI, 1.02-1.10; *P* = .001) (Table 3).

Discussion

The present study examined a large population-based cohort of patients with preexisting IHD who were taking statins and evaluated their clinical outcomes as a function of achieved LDL-C levels. We found that having an LDL-C level of 70.0 mg/dL or less had no statistically significant association with the risk of MACE compared with patients who had LDL-C between 70.1 and 100.0 mg/dL. However, LDL-C level between 70.1 and 100.0 mg/dL was significantly associated with lower risk of MACE when compared with higher LDL-C levels of 100.1 to 130.0 mg/dL. The robustness of these observations is supported by secondary and sensitivity analyses that adjust for differences in baseline characteristics, account for less adherent patients, and examine LDL-C as a continuous exposure through spline analysis. In the spline analysis,

Table 3. Sensitivity Analyses of the Hazard Ratio (HR) of Major Cardiac Events (MACEs) Comparing Achieved Low vs Moderate and Moderate vs High Levels of Low-Density Lipoprotein Cholesterol (LDL-C) Excluding All-Cause Mortality and Among Patients With at Least 50% Adherence to Statin Treatment

Analysis	LDL-C Group[a]									
	Low		Moderate		High		Low vs Moderate		Moderate vs High	
	Patients, No.	MACEs, No. (Rate per 1000 Person-years)	Patients, No.	MACEs, No. (Rate per 1000 Person-years)	Patients, No.	MACEs, No. (Rate per 1000 Person-years)	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Excluding All-Cause Mortality										
Unadjusted	9041	2148 (62.6)	16 782	3801 (58.7)	5751	1408 (65.1)	1.06 (1.01-1.12)	.02	0.91 (0.85-0.96)	.001
Adjusted[b]	9041	2148 (62.6)	16 782	3801 (58.7)	5751	1408 (65.1)	0.99 (0.94-1.05)	.82	0.93 (0.87-0.98)	.01
50% Adherent Patients										
Unadjusted	15 495	5076 (88.6)	28 762	8467 (77.3)	10 627	3491 (88.9)	1.15 (1.11-1.19)	<.001	0.87 (0.84-0.91)	<.001
Adjusted[c]	15 495	5076 (88.6)	28 762	8467 (77.3)	10 627	3491 (88.9)	1.06 (1.02-1.10)	.001	0.87 (0.84-0.91)	<.001

Abbreviations: BMI, body mass index; CKD, chronic kidney disease.

SI conversion factor: To convert milligrams per deciliter to millimoles per liter, multiply by 0.0259.

[a] Index LDL-C was grouped as low (≤70.0 mg/dL), moderate (70.1-100.0 mg/dL), or high (100.1-130.0 mg/dL).

[b] Included variables in model: age, sex, ethnicity, socioeconomic status, smoking status, diabetes, insulin use, number of angioplasties, CKD stage, physician visits, Charlson risk score, time taking statins.

[c] Included variables in model: age, sex, ethnicity, socioeconomic status, smoking status, diabetes, insulin use, number of angioplasties, CKD stage, physician visits, Charlson risk score, time taking statins, BMI.

inflections in the relationship between LDL-C and MACE were somewhere below the 100.0 mg/dL knot and above the 70.0 mg/dL knot. Whereas recent editorials have cited that lower LDL-C is better,[11,20] our study of observed LDL-C levels and their association with cardiac outcomes has found only partial support for these claims. In the sensitivity analysis including patients with lower adherence (≥50%), there was slightly increased risk of MACE in the low LDL-C group compared with the moderate LDL-C group. Whereas this may reflect clinical risk of low levels of LDL-C, these results further support the main findings of this study that achieving a level below 70 mg/dL is not beneficial for all patients.

The evidence cited in guidelines for more aggressive treatment of LDL-C levels comes from RCTs and a meta-analysis of RCTs comparing high-intensity statin treatment with lower-intensity treatment. The meta-analysis found that more intensive therapy was associated with an overall proportional risk reduction of 15% (95% CI, 11%-18%; $P < .001$) in MACE compared with less intensive therapy.[3] Neither of the 2 RCTs with significant findings addressed the extent of comorbidities or polypharmacy among their generally younger patients with IHD, which are factors that increasingly affect therapeutic decisions facing physicians.[21(pp257-264)] Furthermore, there are well-documented adverse events, such as myalgia, nephropathy, and onset of diabetes, associated with intensified statin treatment that contribute to clinical considerations in statin regimen management.[22-24] With RCTs focused on treatment efficacy and safety, the evidence from these trials to support claims that lower LDL-C levels are associated with clinical benefit is not yet definitive for everyday community-based practice.

One of the strengths of our study is the incorporation of comorbidities, numbers of concomitant medications, and measures of health care use into our analytical models. Studies demonstrating the relationship between numbers of medications and adherence to medication use emphasize the importance of these variables when treating physicians are deciding on cardiovascular disease regimens.[25,26] In consideration of baseline differences in clinical characteristics between the LDL-C groups (eg, comorbidities and number of long-term medications), PS-matched analyses confirmed our initial findings that no significant additional clinical benefit was associated with achieved LDL-C levels below 70.0 mg/dL. Another consideration is whether the benefits of lowering LDL-C vary by age, as seen in the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) trial results.[8] We examined whether the association between achieved LDL-C level and MACEs differed when stratified by age and found no differences in the significance or direction of associations from our main analyses.

To inform long-term statin management, we included only patients with IHD who had been consistently taking statins for at least 1 year and evaluated LDL-C levels of patients in community-based care. Previous evidence has not always addressed this long-term outlook. One study cited as evidence for more intensive statin therapy measured LDL-C levels during acute hospitalization—a period in which LDL-C levels may fluctuate considerably.[4] This highlights a fundamental difference between RCTs and our study: while RCTs do not usually study prevalent users, these patients were the focus of our research. Our findings of significantly lower risk of MACEs associated with achieved LDL-C level of less than 100.0 mg/dL but not with achieved LDL-C of less than 70.0 mg/dL suggest a target for long-term statin treatment.

Additional analysis examining LDL-C as a continuous exposure in a cubic spline analysis rather than stratifying by predefined LDL-C groups confirmed the results found in our main analyses that achieved LDL-C level of less than 100.0 mg/dL was associated with lower risk of MACEs, but at roughly 90 mg/dL, this protective effect diminished and was no longer significant. In addition to RCTs, 2 retrospective post hoc analyses of RCT data have examined stratified groups of patients with achieved LDL-C levels well below 70 mg/dL and the association with cardiac outcomes.[6,7] One of these studies reported a nonsignificant finding of lower rates of MACEs with LDL-C levels below 100 mg/dL but emphasized that lower LDL-C lev-

els may be due to differences in patient characteristics not assessed in their study rather than greater treatment intensity.[7] The other post hoc study[6] reported that results of achieved LDL-C after 3 months were not found to be significantly associated with lower rates of MACEs. While these have been cited as evidence to support the argument that lower LDL-C levels afford greater protection, our results suggest that at lower levels of LDL-C, the clinical benefit may not be significant.

There are several limitations to consider in this study. To best ensure treatment impact, we included only those patients who were at least 80% adherent to statin therapy during the year prior to the index LDL-C measurement. This limits the generalizability of our results to individuals who are more adherent to statin treatment. We also restricted our study population to patients with preexisting IHD being treated in the community setting, which means that our findings are not necessarily applicable to patients who have had a recent cardiac event. Our categorization of index LDL-C was based on an observed achieved value after at least 1 year of statin treatment; however, this level may not have represented a stable LDL-C over subsequent years. Additional analyses among a subgroup of the study population that had no variability from their index LDL-C over the first follow-up year demonstrated results consistent with our main analyses (results not shown). Further to this point, future research should consider variability of LDL-C as a potential confounder. While using all-cause mortality in our models is a limitation, we have tried to minimize the impact of this by excluding patients with cancer, which is a leading cause of mortality in Israel.[27(pp11-13)] Additionally, although we conducted PS analyses to adjust for baseline differences, it is possible that other confounders were not accounted for in the analyses.

Conclusions

This study of more than 30 000 community-treated patients with IHD who were adherent to statin treatment found lower risk of MACEs associated with achieved LDL-C levels below 100 mg/dL, but no additional benefit was demonstrated with LDL-C below 70 mg/dL. Our results do not provide support for a blanket principle that lower LDL-C is better for all patients in secondary prevention.

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Editor's Note

Low-Density Lipoprotein Cholesterol Levels and Statin Treatment—A Moving Target?

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Statins are a staple of secondary prevention for individuals with stable cardiovascular disease. However, there is controversy on how to determine the right statin dose, and whether it should be based on low-density lipoprotein cholesterol (LDL-C) levels. Guidelines for secondary prevention in individuals with stable cardiovascular disease differ in recommending a statin intensity goal or a particular LDL-C level (typically <70 mg/dL).[1,2] In this issue of *JAMA Internal Medicine*, Leibowitz et al[3] report on more than 31 000 Israeli adults with stable cardiovascular disease and the association between their LDL-C levels with statin use and cardiovascular outcomes. After adjusting for multiple potential confounders, the authors observed that individuals who achieved an LDL-C level of 70 mg/dL or less were no less likely to have major adverse cardiovascular events compared with those who achieved an LDL-C between 70 and 100 mg/dL. Using nonlinear modeling, the authors found that achieving lower LDL-C levels was associated with a decreased risk of cardiovascular events, but only to an LDL-C of roughly 90 mg/dL.

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This retrospective study represents an important effort in clarifying goals for long-term statin therapy. The findings suggest that targeting an LDL-C level of less than 100 mg/dL achieves the same cardiovascular risk reduction as more aggressive LDL-C targets, which could help to minimize adverse effects that are more common with higher statin doses needed for lower LDL targets while maximizing benefits. The finding of improved outcomes below a threshold LDL-C level also supports consideration of absolute LDL-C levels instead of relative LDL-C percentage reductions for gauging an adequate response to statin therapy and raises questions about the practice of statin dosing by intensity. The study by Leibowitz et al[3] adds important information to the ongoing discussion of the best statin strategy and LDL-C targets to improve outcomes with minimal harms.

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