LDL Cholesterol Response and Statin Adherence Among High-Risk Patients Initiating Treatment

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ABSTRACT

Objectives: The 2013 American College of Cardiology (ACC)/American Heart Association (AHA) cholesterol treatment guideline recommends monitoring percent reduction in low-density lipoprotein cholesterol (LDL-C) among patients initiating statins as an indication of response and adherence. We examined LDL-C reduction and statin adherence among high-risk patients initiating statins in a real-world setting.

Study Design: Retrospective cohort study.

Methods: The study population included Kaiser Permanente Georgia members (n = 1066) with a history of coronary heart disease or risk equivalent(s) initiating statins in 2011. Percent change in LDL-C was defined using measurements before and 60 to 450 days after statin initiation. Statin adherence was defined by proportion of days covered, categorized as high (≥80%), intermediate (50%-79%), and low (<50%).

Results: Overall, 58.4% of patients failed to achieve a ≥30% LDL-C reduction after statin initiation. The prevalences of high, intermediate, and low statin adherence were 41.3%, 23.2%, and 35.6%, respectively. Of patients with high adherence, 42.3% did not achieve a ≥30% reduction in LDL-C compared with 54.7% and 79.7% of those with intermediate and low statin adherence, respectively. After multivariable adjustment, and compared with those with high adherence, the risk ratios for not achieving a ≥30% LDL-C reduction were 1.31 (95% CI, 1.13-1.52) and 1.88 (95% CI, 1.67-2.11), for those with intermediate and low adherence. Women and African Americans were less likely to have high adherence, whereas having cardiologist visits was associated with high adherence.

Conclusions: In a real-world setting, many patients did not achieve a 30% or larger LDL-C reduction. These data support the ACC/AHA recommendation to monitor LDL-C response among patients initiating statins.

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Reducing low-density lipoprotein cholesterol (LDL-C) has long been a central component of coronary heart disease (CHD) risk reduction, particularly among high-risk individuals.[1] The use of statins has increased markedly among US adults over the past 2 decades and this has been recognized as a major contributor to the decline in CHD in the US population.[2] However, despite the increased use of statins, substantial treatment gaps persist.

The 2013 American College of Cardiology (ACC)/American Heart Association (AHA) Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults[3] noted that the magnitude of LDL-C reduction (30%-50% and ≥50% reductions for patients initiating moderate-intensity and high-intensity statins, respectively) should be used as a means to identify patients who may not be sufficiently adherent to their statin. This percent reduction is largely based on findings from meta-analyses of randomized controlled trials of statin therapy.[4] However, patients in randomized trials represent select groups and there are limited data describing the reduction in LDL-C observed for patients initiating statins in real-world settings. Additionally, low statin adherence is common, and the degree to which low statin adherence accounts for smaller than expected reductions in LDL-C among patients with high-CHD risk is not well studied.[5-7]

We conducted a retrospective cohort study of high-risk patients to examine LDL-C response following the initiation of statin treatment. Additionally, we investigated the contribution of statin adherence to achievement of a 30% or larger reduction in LDL-C following statin initiation. As part of these analyses, we determined the factors associated with statin nonadherence and the factors beyond adherence that were associated with failure to achieve a 30% or larger reduction in LDL-C following statin initiation.

METHODS

Take-Away Points

- Using real-world clinical data, our study demonstrated that nonadherence to statins was very common (>50%) among high-risk patients initiating statins. Nonadherence was associated with suboptimal low-density lipoprotein cholesterol (LDL-C) reduction.
- Even among patients with high adherence, a small LDL-C response (<30%) to statins was very common.
- LDL-C should be monitored following statin initiation to identify suboptimal LDL-C response and medication nonadherence.

Data Source

The current study was conducted at Kaiser Permanente Georgia (KPGA), an integrated healthcare delivery system serving approximately 235,000 members in the greater metropolitan Atlanta area. KPGA maintains comprehensive electronic medical records (EMRs) and other electronic databases that capture nearly 100% of their members' health services utilization. Members of KPGA are highly representative of its service areas.[8]

Study Population

We included KPGA patients who initiated a statin in 2011 (Figure 1). The date of each patient's first statin fill in 2011 was defined as their "index date." The "baseline period" was defined as the 365 days prior to the index date. The "follow-up period" was defined as the time between the index date and a patients' last available LDL-C measurement on or before March 31, 2012.

To be eligible for this analysis, KPGA patients had to have: 1) been 18 years or older on January 1, 2011; 2) not been pregnant during the time between their index date and March 31, 2012; 3) filled at least 1 statin in 2011; 4) continuous health plan enrollment with drug benefits during the baseline and follow-up periods; 5) an LDL-C measurement performed at least 60 days following the index statin fill (for patients with statin prescriptions containing 30 days of supply [>120 and 180 days following the index date for patients receiving 60 and 90 days of supply, respectively]) but on or before March 31, 2012; 6) at least 1 LDL-C measurement during the baseline period; and 7) data on all National Cholesterol Education Program Adult Treatment Panel III (ATP III) risk factors (ie, age, total cholesterol, high-density lipoprotein cholesterol [HDL-C], systolic blood pressure, antihypertensive medication use, smoking, history of CHD, history of diabetes, peripheral artery disease and abdominal aortic aneurysm) from the baseline period.

We excluded patients with any statin fills during the baseline period and restricted our analysis to high-risk patients (ie, those with a history of CHD or a CHD risk equivalent). CHD risk equivalents included diabetes, history of stroke, a 10-year CHD risk greater than 20% based on the Framingham Risk Score, and other forms of symptomatic atherosclerotic disease including peripheral arterial disease, abdominal aortic aneurysm, and carotid artery disease.[1]

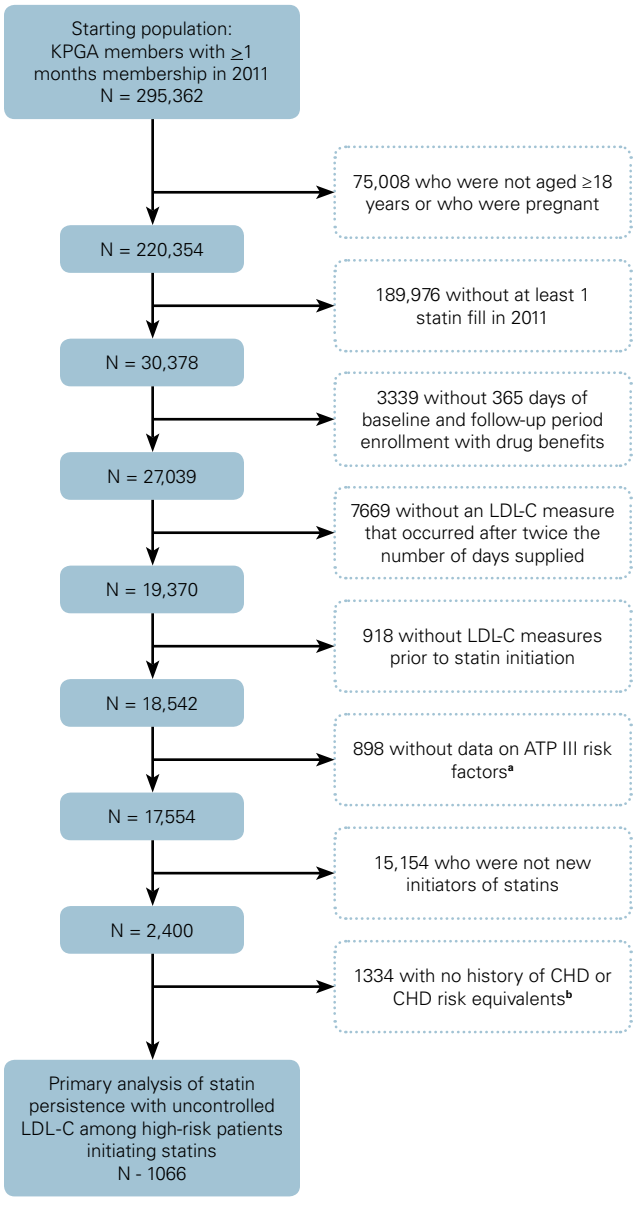
Statin adherence. Statin adherence was defined using the proportion of days covered (PDC). We calculated the PDC as the cumulative number of days for which the patient had a statin available to take between their first fill in 2011 and their last LDL-C measurement during follow-up divided by the total number of days in this interval. The days of supply for statins that each patient had was a cumulative sum of days' supply from all statin medications regardless of whether the patient changed statin dose or type. In several prior studies of medication adherence using pharmacy fill data, patients with medications available to take on 80% or more days have been categorized as adherent.[9-11] Adherence based on this cut point for cardiovascular disease–related conditions has been associated with improved outcomes.[12-14] Additionally, the 80% threshold for defining high adherence is recommended by CMS, the Pharmacy Quality Alliance, and the National Quality Forum.[15-18] We categorized adherence as high (PDC ≥80%), intermediate (PDC 50%-79%), or low (PDC <50%).[12,19,20] We used PDC to define medication adherence because it provides more conservative estimates than the medication possession ratio.[21]

LDL-C levels. Total cholesterol, HDL-C, and triglycerides were measured at KPGA laboratories as part of a lipid panel following standard measurement procedures. The LDL-C measures were direct measures or calculated using the Friedewald equation.[22] Percent change in LDL-C was calculated as the difference between baseline and follow-up LDL-C divided by baseline LDL-C (defined using measurements before and 60 to 450 days after statin initiation). Our primary outcome was having a small reduction in LDL-C, defined as a change in LDL-C less than 30%. A secondary outcome—uncontrolled LDL-C—was defined as an LDL-C 100 mg/dL or greater at the last LDL-C measured on or before March 31, 2012. It is important to note that although the LDL-C target of less than 100 mg/dL is no longer recommended by the 2013 ACC/AHA cholesterol treatment guideline,[3] it is included in this analysis as a secondary outcome for comparison purposes.

Study Variables

Study variables were chosen according to a conceptual framework[23] describing how factors interact to influence medication adherence.

Figure 1. Exclusion Cascade of Study Population



ATP III indicates Adult Treatment Panel III; CHD, coronary heart disease; KPGA, Kaiser Permanente Georgia; LDL-C, low-density lipoprotein cholesterol.
[a]National Cholesterol Education Program, Adult Treatment Panel III risk factors: age, total cholesterol, high-density lipoprotein cholesterol, systolic blood pressure, antihypertensive medication use, smoking, history of CHD, history of diabetes, peripheral artery disease, and abdominal aortic aneurysm.
[b]CHD risk equivalents: Framingham risk score >20%, diabetes, history of stroke/carotid disease, history of peripheral vascular disease, and history of abdominal aortic aneurysm.

Patient factors. Demographic information (ie, age, sex, self-reported race) was obtained from Kaiser Permanente's EMR database. Area-level income was determined by matching patients' geocoded addresses to 2010 Census data at the census tract level. Smoking status was obtained from the EMR as a self-reported response to whether patients currently smoke cigarettes. History of CHD, diabetes, stroke/carotid disease, and peripheral artery disease (PAD) or abdominal aneurysm were defined by *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) diagnostic codes obtained from KPGA's claims database. In addition, hospitalizations during the baseline period were enumerated as a measure of patient health. Medication characteristics (ie, number of medications dispensed, type of statin, statin dose titration, number of statin refills, and use of a high-dose statin) were obtained from the KPGA pharmacy database. Statin type was defined based on the fill most recent to, and preceding, the last LDL-C measurement during follow-up. Statin titration was defined as an upward change in statin dose equivalents (**eAppendix Table 1** [eAppendices available at **www.ajmc.com**]).[24-26] High-intensity statins were defined as 80 mg of simvastatin, 40 or 80 mg of atorvastatin, or 20 or 40 mg of rosuvastatin, according to the 2013 ACC/AHA cholesterol treatment guideline.[3]

The presence of CHD or CHD risk equivalents were defined by *ICD-9-CM* diagnostic codes during the baseline period and published algorithms (**eAppendix Table 2**). For patients without CHD or risk equivalents, the Framingham CHD risk score was calculated using the ATP III point scoring system and measurements from the patients' EMRs from the baseline period.[1]

Provider factor. Patients' cardiologist visits were assessed during the follow-up period.

Statistical Analysis

Patient characteristics and percent change in LDL-C were calculated overall and by level of statin adherence. Risk ratios for a reduction in LDL-C <30% and uncontrolled LDL-C associated with low and intermediate versus high statin adherence, were calculated separately using log-binomial regression models with 3 levels of adjustment. An initial model adjusted for age, race, and sex. A second model included additional adjustment for area-level income, smoking, diabetes, history of stroke/carotid disease, Framingham 10-year CHD risk score of less than 20%, history of PAD or abdominal aneurysm, type of statin, number of medications, use of a high-dose statin, titration of statin dose, and cardiologist care. A final model additionally included adjustment for baseline LDL-C.

We conducted sensitivity analyses to examine the robustness of the findings. We examined the adjusted relative risk of a small LDL-C reduction (<30%) associated with statin adherence, restricting the cohort to: 1) patients

with a 30-day supply for their initial statin fill, and 2) restricting the cohort to patients with at least 2 measurements of LDL-C measures during the follow-up period (and defining a small reduction in LDL-C as less than 30% on each of the last 2 measurements). Additionally, we calculated adjusted risk ratios for having intermediate/low statin adherence (PDC <80% vs ≥80%). Statistical analyses were conducted using SAS version 9.1.3 (SAS Institute, Cary, North Carolina).

RESULTS

Patient Characteristics

A total of 1066 KPGA patients with CHD or risk equivalents who initiated statin therapy in 2011 were included in our primary analysis. Older patients were more likely, whereas females and African-Americans were less likely, to have high adherence to statins (Table 1). Also, patients with an area-level income of $75,000 or more, a history of CHD, taking at least 10 different medications, with a cardiologist visit during follow-up, titration to their statin dose during follow-up, and with at least 1 statin refill in 2011 were more likely to have high adherence to statins.

Statin Adherence and Reduction in LDL-C

Over a median follow-up time of 213 days, 58.4% of patients failed to achieve at least a 30% reduction in LDL-C. Mean LDL-C reductions of 55.9 mg/dL (SD = 34.6 mg/dL), 44.6 mg/dL (SD = 35.8 mg/dL), and 21.0 mg/dL (SD = 37.1 mg/dL) were achieved for patients with high, intermediate, and low statin adherence, respectively (Figure 2). Small LDL-C reductions (<30%) were observed for 42.3%, 54.7%, and 79.7% of participants with high, intermediate, and low statin adherence, respectively (Table 2). After multivariable adjustment, relative to high adherence, intermediate adherence was associated with a 31% (risk ratio [RR], 1.31; 95% CI, 1.13-1.52) increased risk of a small LDL-C reduction, and low adherence was associated with an 88% (RR, 1.88; 95% CI, 1.67-2.11) increased risk of a small LDL-C reduction. The associations were consistent when we restricted the study cohort to patients with 30-day statin prescriptions (eAppendix Table 3) and

Table 1. Characteristics of Patients at High Risk for Coronary Heart Disease Initiating Statins, by Level of Statin Adherence During Follow-up (data presented as numbers and row percents)

	Adherence With Statins			
	High (PDC ≥80%)	Intermediate (PDC = 50%-79%)	Low (PDC <50%)	Total Cohort
N (%)	440 (41.3)	247 (23.2)	379 (35.6)	1066 (100)
Variables[a] from the baseline period				
Age, years				
<40	17 (27.0)	11 (17.5)	35 (55.6)	63 (5.9)
40-64	285 (40.0)	172 (24.2)	255 (35.8)	712 (66.8)
≤65	138 (47.4)	64 (22.0)	89 (30.6)	291 (27.3)
Race				
White	231 (53.6)	93 (21.6)	107 (24.8)	431 (40.4)
African American	166 (31.4)	127 (24.1)	235 (44.5)	528 (49.5)
Other/unknown	43 (40.2)	27 (25.2)	37 (34.6)	107 (10.0)
Sex				
Female	163 (35.1)	117 (25.2)	184 (39.7)	464 (43.5)
Male	277 (46.0)	130 (21.6)	195 (32.4)	602 (56.5)
Area-level income, $				
<30,000	33 (42.9)	17 (22.1)	27 (35.1)	77 (7.2)
30,000-<45,000	77 (35.8)	57 (26.5)	81 (37.7)	215 (20.2)
45,000-<60,000	151 (40.8)	76 (20.5)	143 (38.7)	370 (34.7)
60,000-<75,000	115 (41.5)	67 (24.2)	95 (34.3)	277 (26.0)
≥75,000	64 (50.4)	30 (23.6)	33 (26.0)	127 (11.9)

(continued)

Table 1. Characteristics of Patients at High Risk for Coronary Heart Disease Initiating Statins, by Level of Statin Adherence During Follow-up (data presented as numbers and row percents) *(continued)*

	Adherence With Statins			
	High (PDC ≥80%)	Intermediate (PDC = 50%-79%)	Low (PDC <50%)	Total Cohort
Nonsmoker	366 (42.4)	192 (22.3)	305 (35.3)	863 (81.0)
Smoker	74 (36.5)	55 (27.1)	74 (36.5)	203 (19.0)
LDL-C[b]				
<100 mg/dL	77 (46.4)	36 (21.7)	53 (31.9)	166 (15.6)
100-129 mg/dL	141 (43.1)	68 (20.8)	118 (36.1)	327 (30.7)
≥130 mg/dL	222 (38.7)	143 (25.0)	208 (36.3)	573 (53.8)
History of CHD[c]	127 (52.7)	60 (24.9)	54 (22.4)	241 (22.6)
No history of CHD	313 (37.9)	187 (22.7)	325 (39.4)	825 (77.4)
History of diabetes[c]	286 (38.7)	174 (23.5)	279 (37.8)	739 (69.3)
No history of diabetes	154 (47.1)	73 (22.3)	100 (30.6)	327 (30.7)
History of stroke/carotid disease	19 (40.4)	12 (25.5)	16 (34.0)	47 (4.4)
No history of stroke/carotid disease	421 (41.3)	235 (23.1)	363 (35.6)	1019 (95.6)
Framingham risk score ≥20%	97 (49.0)	38 (19.2)	63 (31.8)	198 (18.6)
Framingham risk score <20%	343 (39.5)	209 (24.1)	316 (36.4)	868 (81.4)
History of PAD or abdominal aneurysm	44 (45.8)	19 (19.8)	33 (34.4)	96 (9.0)
No history of PAD or abdominal aneurysm	396 (40.8)	228 (23.5)	346 (35.7)	970 (91.0)
Number of different medications dispensed[d]				
<5	70 (35.2)	41 (20.6)	88 (44.2)	199 (18.7)
5-9	222 (40.4)	122 (22.2)	205 (37.3)	549 (51.5)
≥10	148 (46.5)	84 (26.4)	86 (27.0)	318 (29.8)
Type of statin[e]				
Simvastatin	283 (40.8)	146 (21.0)	265 (38.2)	694 (65.1)
Lovastatin	44 (42.3)	26 (25.0)	34 (32.7)	104 (9.8)
Pravastatin	67 (41.1)	42 (25.8)	54 (33.1)	163 (15.3)
Other	46 (43.8)	33 (31.4)	26 (24.8)	105 (9.9)
Variables from the follow-up period				
No cardiologist visit	296 (37.3)	189 (23.8)	309 (38.9)	794 (74.5)
Cardiologist visit	144 (52.9)	58 (21.3)	70 (25.7)	272 (25.5)
No statin dose titration	378 (40.7)	196 (21.1)	354 (38.2)	928 (87.1)
Statin dose titration	62 (44.9)	51 (37.0)	25 (18.1)	138 (13.0)
Hospitalized	32 (37.2)	25 (29.1)	29 (33.7)	86 (8.1)
Not hospitalized	408 (41.6)	222 (22.7)	350 (35.7)	980 (91.9)
≥1 statin refill	440 (50.1)	247 (28.1)	192 (21.8)	879 (82.5)
No statin refills	0	0	187 (100)	187 (17.5)
High-dose statin	67 (37.4)	44 (24.6)	68 (38.0)	179 (16.8)
Low-/moderate-dose statin	373 (42.1)	203 (22.9)	311 (35.1)	887 (83.2)

CHD indicates coronary heart disease; LDL-C, low-density lipoprotein cholesterol; PAD, peripheral artery disease; PDC, proportion of days covered.
[a]Variables measured during 365 days prior to first statin dispensing in 2011 unless otherwise specified.
[b]Most recent LDL-C measure in the 365 days prior to index statin fill.
[c]History of disease in the period 365 days prior to index date through outcome date.
[d]Medications dispensed in the period 365 days prior to index date through outcome date.
[e]Includes combination products containing a statin.

when we required a reduction in LDL-C <30% on the last 2 measurements during follow-up (eAppendix Table 4).

Other Factors Associated With a Reduction in LDL-C <30%

In age, race, and sex-adjusted models, African Americans and patients who were taking pravastatin were more likely to have a small reduction in LDL-C compared with whites and patients taking simvastatin, respectively (eAppendix Table 5). Conversely, patients with baseline LDL-C 100 mg/dL or greater and those who had their statin dose titrated during follow-up were less likely to have a small reduction in LDL-C compared with patients with baseline LDL-C less than 100 mg/dL and those who did not have their statin dose titrated, respectively. In the full multivariable adjusted model, African American race was no longer independently associated with a small reduction in LDL-C.

Statin Adherence and LDL-C Control

At the end of follow-up, 44.7% of patients had uncontrolled LDL-C (ie, LDL-C ≥100 mg/dL). The prevalence of uncontrolled LDL-C was 25.7%, 45.3%, and 66.5% among patients with high, intermediate, and low statin adherence, respectively (Table 2, bottom panel). After multivariable adjustment, and compared with high adherence, intermediate and low statin adherence were associated with a risk ratio for uncontrolled LDL-C of 1.64 (95% CI, 1.34-2.02) and 2.44 (95% CI, 2.06-2.89), respectively.

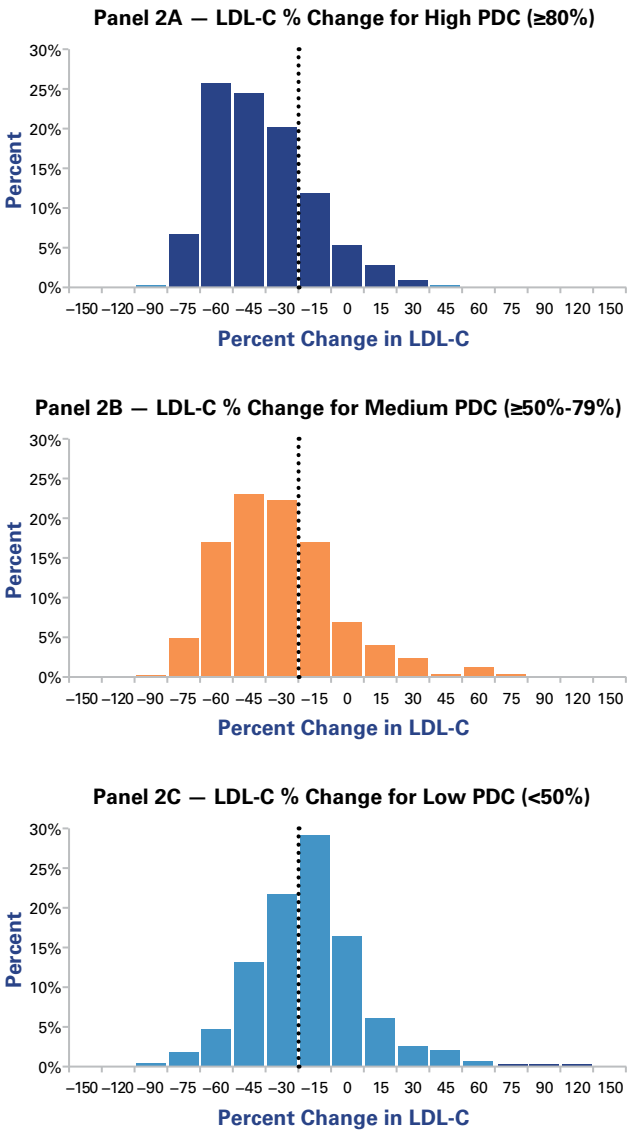
Factors Associated With Intermediate/Low Statin Adherence

In age, race, and sex-adjusted models, being aged at least 65 years, having a history of CHD, taking 5 to 9 or more than 10 medications, or seeing a cardiologist following statin initiation were each associated with a reduced risk of intermediate/low statin adherence (PDC <80%) (Table 3). Women, African Americans, and smokers were more likely to have intermediate/low statin adherence. After full multivariable adjustment, patients taking 10 or more medications at baseline and seeing a cardiologist during the follow-up period decreased the risk of intermediate/lower statin adherence and being female, African American, or hospitalized during the follow-up period increased the risk of intermediate/low adherence.

DISCUSSION

In this study, the majority of patients with CHD or CHD risk equivalents did not achieve a 30% or larger reduction in LDL-C approximately 1 year following statin initiation. Additionally, most patients had moderate or low statin adherence. We observed that adherence was strongly associated with LDL-C reduction, with about half of those with moderate adherence, and less than a quarter of those with low adherence, demonstrating a LDL-C reduction expected for a moderate intensity statin regimen. These findings show that statin nonadherence in real-world clinical care is very common and has a ma-

Figure 2. Percent Change in LDL-C Between Baseline and Follow-up Periods Among High-Risk Patients Initiating Statins, by Level of Statin Adherence



LDL-C indicates low-density lipoprotein cholesterol; PDC, proportion of days covered.

Table 2. Percentage and Adjusted Risk Ratios for Reduction in LDL-C <30% and Uncontrolled LDL-C Associated With Statin Adherence Among High-Risk KPGA Patients Initiating Statins

Outcomes	Adherence With Statins: High (PDC ≥80%)	Intermediate (PDC = 50%-79%)	Low (PDC <50%)	*P* Trend
Reduction in LDL-C <30%				
n (%)	186 (42.3)	135 (54.7)	302 (79.7)	<.01
Risk ratios (95% CI)				
Model 1[a]	1 (ref)	1.30 (1.11-1.52)	1.89 (1.67-2.14)	<.01
Model 2[b]	1 (ref)	1.29 (1.10-1.51)	1.85 (1.64-2.10)	<.01
Model 3[c]	1 (ref)	1.31 (1.13-1.52)	1.88 (1.67-2.11)	<.01
Uncontrolled LDL-C[d]				
n (%)	113 (25.7)	112 (45.3)	252 (66.5)	<.01
Risk ratios (95% CI)				
Model 1[a]	1 (ref)	1.73 (1.40-2.14)	2.52 (2.11-3.01)	<.01
Model 2[b]	1 (ref)	1.68 (1.36-2.08)	2.48 (2.08-2.96)	<.01
Model 3[c]	1 (ref)	1.64 (1.34-2.02)	2.44 (2.06-2.89)	<.01

KPGA indicates Kaiser Permanente Georgia; LDL-C, low-density lipoprotein cholesterol; PDC, proportion of days covered; ref, reference.
[a]Model 1 includes adjustment for age, race, and sex.
[b]Model 2 includes adjustment for age, race, sex, type of statin, income, smoking, number of medications, diabetes, history of stroke/carotid disease, Framingham risk score >20%, history of abdominal aneurysm during the baseline period and taking a high-dose statin, statin dose titration, cardiologist care during follow-up, and hospitalization during follow-up.
[c]Model 3 includes variables in Model 2 and LDL-C prior to the index statin fill.
[d]LDL-C ≥100 mg/dL at follow-up.

jor impact on LDL-C reduction. Also, even among patients with high adherence, 42.3% failed to achieve a 30% reduction in LDL-C approximately 1 year following statin initiation.

The results from the current study highlight the role of statin nonadherence in suboptimal LDL-C reduction. Compared with those with high adherence, patients with low statin adherence were almost twice as likely to have a small (<30%) reduction in LDL-C, after adjusting for potential confounders. Although these results are consistent with previous research,[27-29] our study points to a uniquely important issue: in well-managed patients with access to healthcare and a comprehensive system of services aimed at providing easy and convenient means for filling prescriptions, statin adherence remains low.

The reasons for statin nonadherence are likely multifactorial and include patient, provider, and health system factors.[30-34] Consistent with prior studies,[5,35] women and African Americans were more likely to have low statin adherence. Women may have more depressive symptoms, be less satisfied with communication with their healthcare provider, and/or have inadequate social support systems in place compared with men.[36] Racial differences in statin adherence may be due to patient health beliefs, social norms, preferences, knowledge about the benefits of statins, or patient–physician communication.[37] In the current study, patients who had a cardiologist visit during follow-up were less likely to have low statin adherence. We were not able to discern whether cardiologists are more active in monitoring and encouraging statin adherence or whether patients in this health system who see cardiologists are more motivated to be adherent. Finally, there may be reasons for nonadherence related to the statin treatment itself. Statin-related events, such as muscle aches or weakness, gastrointestinal symptoms, and liver enzyme abnormalities, are reported in 5% to 10% of patients in trials, and as high as 20% of patients in observational studies.[38] The role of patient intolerance as a contributor to poor adherence and discontinuation has not been fully characterized.

Even among patients with high adherence in the current study, a substantial proportion (42.3%) did not have a 30% reduction in LDL-C. Additionally, 25.7% of patients with high adherence did not achieve an LDL-C less than 100 mg/dL at the end of follow-up. The expectation of a 30% or larger reduction in LDL-C associated with low-moderate intensity statins is derived from a meta-analysis of randomized controlled trials.[4] Given the strong graded association between higher on-treatment LDL-C and increased cardiovascular disease risk, the small reduction in LDL-C experienced by many patients—even for those with high adherence—represents an important clinical challenge.[39] However, reductions in LDL-C not reaching 30% may nevertheless be important in reducing the risk of cardiovascular events and associated morbidity and healthcare costs.[40-42] Future studies are needed to evaluate the excess cardiovascular disease risk, if any, associated with having a suboptimal reduction in LDL-C following the initiation of statins.

Strengths and Limitations

Strengths of the current study include its diverse, real-world population of high-risk patients initiating statin therapy. Additionally, our study utilized EMR data that included pharmacy claims. In a recent unpublished survey, 95.1% of KPGA members reported that they never or rarely fill their prescriptions at non-network pharmacies (results obtained via personal communication with A. Owen-Smith, PhD). Therefore, our study likely reflects nearly complete capture of statins filled by patients.

Several potential limitations of the current study warrant mentioning. Our measure of statin adherence was based on pharmacy fill data and may not represent actual medication consumption.[43] Although only 13% of patients had their statin dose titrated during follow-up, it is possible that changes in statin dose or type during follow-up may have altered adherence estimates. Given the observational study design, confounding due to unmeasured risk factors may be present. The follow-up period was relatively short and we were not able to examine the long-term effects of statin nonadherence on percent change in LDL-C or CHD outcomes. Consistent with prior studies, a low percentage of patients initiated statins at high doses, which prevented us from studying LDL-C response to high-dose statins. Finally, it is possible that due to limitations of administrative data, some misclassification for study variables may be present.

CONCLUSIONS

More than half of patients with a high risk for CHD who are initiating statins demonstrated statin nonadherence, which was associated with failure to achieve at least a 30% reduction in LDL-C. Additionally, a substantial percentage of patients with high statin adherence still did not achieve a 30% reduction in LDL-C. The findings from our study support the 2013 ACC/AHA cholesterol treatment guideline that suggests monitoring LDL-C following initiation of statins for response and poor adherence.

Table 3. Adjusted Risk Ratios for Intermediate/Low Versus High Adherence (PDC <80% vs ≥80%) to Statins Among High-Risk KPGA Patients Initiating Statins

	Age, Race, Sex Adjusted		Full Multivariable Adjusted[a]	
Factor	Risk Ratio	95% CI	Risk Ratio	95% CI
Age, years				
<40	1	ref	1	ref
40-64	0.85	(0.73-1.00)	0.90	(0.77-1.05)
≥65	0.79	(0.66-0.95)	0.87	(0.73-1.05)
Female sex	1.15	(1.04-1.26)	1.15	(1.04-1.28)
Race				
White	1	ref	1	ref
African American	1.42	(1.26-1.60)	1.39	(1.24-1.57)
Other/unknown	1.26	(1.04-1.52)	1.23	(1.02-1.48)
LDL-C[b]				
<100 mg/dL	1	ref	1	ref
100-129 mg/dL	1.01	(0.86-1.20)	1.01	(0.85-1.19)
≥130 mg/dL	1.06	(0.91-1.24)	1.03	(0.89-1.21)
History of CHD[c]	0.83	(0.71-0.95)	0.88	(0.74-1.03)
Smoking	1.13	(1.00-1.26)	1.11	(0.98-1.24)
Area-level income, $				
≥75,000	1	ref	1	ref
60,000-<75,000	1.08	(0.89-1.32)	1.10	(0.90-1.34)
45,000-<60,000	1.05	(0.86-1.27)	1.06	(0.88-1.29)
30,000-<45,000	1.10	(0.90-1.35)	1.12	(0.91-1.37)
<30,000	0.90	(0.68-1.18)	0.90	(0.69-1.18)
Missing	1.24	(0.79-1.95)	1.23	(0.77-1.96)
Total number of medications dispensed[d]				
<5	1	ref	1	ref
5-9	0.89	(0.79-1.01)	0.90	(0.80-1.02)
≥10	0.80	(0.69-0.93)	0.82	(0.70-0.95)
Type of statin[d]				
Simvastatin	1	ref	1	ref
Lovastatin	1.01	(0.85-1.20)	1.04	(0.88-1.24)
Pravastatin	1.04	(0.90-1.19)	1.02	(0.86-1.21)
Other	0.97	(0.82-1.15)	1.08	(0.88-1.33)
Statin dose titration	0.94	(0.81-1.09)	0.96	(0.80-1.16)
Cardiologist care	0.80	(0.70-0.92)	0.83	(0.71-0.97)
Hospitalized between index and outcome dates	1.11	(0.94-1.31)	1.26	(1.07-1.50)
High-dose statin	1.08	(0.95-1.22)	1.10	(0.94-1.28)

CHD indicates coronary heart disease; KPGA, Kaiser Permanente Georgia; LDL-C, low-density lipoprotein cholesterol; PDC, proportion of days covered; ref, reference.
[a]Full multivariable adjustment includes all variables simultaneously.
[b]Most recent LDL-C measure in the 365 days prior to index.
[c]History of disease in the period 365 days prior to index date through outcome date.
[d]Medications dispensed in the period 365 days prior to index date through outcome date.

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eAppendix

Table 1. Equivalent Doses of Statins in the US Market[1,2]

Dose (mg of agent)						
Atorvastatin	Pitavastatin	Simvastatin	Lovastatin	Pravastatin	Fluvastatin	Rosuvastatin
–	–	10	20	20	40	–
10	1	20	40	40	80	5
20	2	40	80	80	–	10
40	4	80	–	–	–	20
80	–	–	–	–	–	40

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Table 2. *ICD-9-CM* Code Definitions for Conditions Used in the Analysis

Condition	Definition
Coronary heart disease	Any one of the following: ● *ICD-9-CM* diagnosis of acute MI (410.XX), unstable angina (411.1, 411.81, 411.89), or CAD (412.00, 413.XX, 414.XX) ● A claim for coronary catheterization, percutaneous coronary intervention, (angioplasty or stent; CPT codes 92980-92996 or *ICD-9-CM* procedure codes 00.66, 36.01-36.09) ● CABG surgery (CPT codes 33510-33536 or *ICD-9-CM* procedure codes 36.10-36.19).
History of diabetes at baseline	At least 2 diagnoses, prescription, or laboratory criteria or combination of any 2 within 12 months: ● *ICD-9-CM* diagnosis: 250, 357.2, 362.0, 648.0, 648.8, 366.41 at family practice, internal medicine, or pediatrics department ● Prescription: dispensing for oral antidiabetic medications or diabetes devices (GPI code 27 or 9720) ● Laboratory: A1C ≥7%
History of abdominal aortic aneurism	Either one of the following: ● At least 1 inpatient claim with *ICD-9-CM* diagnoses (any position) of 441.3-441.9 or CPT codes 34800-34834 or *ICD-9-CM* procedure codes 38.44, 39.25, or 39.71 ● At least 2 carrier claim, carrier line or outpatient claims on separate calendar days with *ICD-9-CM* diagnoses (any position) of 441.3-441.9
History of peripheral arterial disease	Any one of the following: ● At least 1 inpatient claim with *ICD-9-CM* diagnoses (primary diagnosis) of 440.20-440.24, 440.31, 444.2, 443.9, 444.2, or 444.81 ● At least 2 carrier claim, carrier line or outpatient claims on separate calendar days with *ICD-9-CM* diagnoses (primary diagnosis) of 440.20-440.24, 440.31, 444.2, 443.9, 444.2, or 444.81 ● At least 1 claim in any file type with CPT code 37205 or 75962
History of carotid artery disease	Either one of the following: ● At least 1 inpatient claim with *ICD-9-CM* diagnoses (primary diagnosis) of 433.10, 433.11, 433.30, 433.31, or CPT code 35301, 37215, 37216, or *ICD-9-CM* procedure code 00.61 or 00.63 ● At least 2 carrier claim, carrier line or outpatient claims on separate calendar days with *ICD-9-CM* diagnoses (primary diagnosis) 433.10, 433.11, 433.30, 433.31, or CPT code 35301, 37215, 37216, or *ICD-9-CM* procedure code 00.61 or 00.63

A1C indicates glycated hemoglobin; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CPT, Current Procedural Terminology; GPI, Generic Product Identifier; *ICD-9-CM*, *International Classification of Diseases, Ninth Revision, Clinical Modification.*

Table 3. Percentage and Adjusted Risk Ratios for a Reduction In LDL-C <30% Associated With Statin Persistence in Analyses Restricted to Patients With a 30 Days of Supply on Their Initial Statin Fill

	Persistence With Statins			
	High (PDC ≥80%)	**Intermediate (PDC = 50%-79%)**	**Low (PDC <50%)**	***P* Trend**
Patients with 30-day statin supply	N = 329	N = 192	N = 315	
Reduction in LDL-C <30%, n (%)	125 (38.0)	95 (49.5)	252 (80.0)	<.01
Risk ratio (95% CI)				
Model 1[a]	1 (ref)	1.30 (1.07-1.59)	2.10 (1.80-2.44)	<.01
Model 2[b]	1 (ref)	1.31 (1.07-1.60)	2.07 (1.78-2.42)	<.01
Model 3[c]	1 (ref)	1.32 (1.09-1.59)	2.08 (1.80-2.41)	<.01

LDL-C indicates low-density lipoprotein cholesterol; PDC, proportion of days covered; ref, reference.
[a]Model 1 includes adjustment for age, race, and sex.
[b]Model 2 includes adjustment for age, race, sex, type of statin, income, smoking, number of medications, diabetes, history of stroke/carotid disease, Framingham risk score >20%, history of abdominal aneurysm, and taking a high dose statin, statin dose titration, cardiologist care, and hospitalization during follow-up.
[c]Model 3 includes variables in Model 2 and LDL-C prior to the index statin fill.

Table 4. Percentage and Adjusted Risk Ratios for a Reduction in LDL-C <30% at the Last 2 Visits During Follow-up

	Adherence to Statins			
	High (PDC ≥80%)	**Intermediate (PDC = 50%-79%)**	**Low (PDC <50%)**	***P* Trend**
Population with 2 LDL-C measurements[a]	N = 227	N = 153	N = 162	
Reduction in LDL-C <30%, n (%)	67 (29.5)	58 (37.9)	105 (64.8)	<.01
Risk ratios (95% CI)				
Model 1[b]	1 (ref)	1.29 (0.97-1.71)	2.21 (1.74-2.80)	<.01
Model 2[c]	1 (ref)	1.30 (0.97-1.73)	2.14 (1.69-2.70)	<.01
Model 3[d]	1 (ref)	1.39 (1.07-1.81)	2.31 (1.83-2.91)	<.01

LDL-C indicates low-density lipoprotein cholesterol; PDC, proportion of days covered.
[a]Limited to patients with at least 2 measures of LDL-C during follow-up (including the outcome LDL-C and the LDL-C measured prior to the outcome LDL-C).
[b]Model 1 includes adjustment for age, race, and sex.
[c]Model 2 includes adjustment for age, race, sex, type of statin, income, smoking, number of medications, diabetes, history of stroke/carotid disease, Framingham risk score >20%, history of abdominal aneurysm, and taking a high-dose statin, statin dose titration, cardiologist care, and hospitalization during follow-up.
[d]Model 3 includes variables in Model 2 and LDL-C prior to the index statin fill.

Table 5. Adjusted Risk Ratios for a Reduction in LDL-C <30% Associated With Risk Factors Among High-Risk KPGA Patients Initiating Statins

	Age, Race, Sex (adjusted)		Full Multivariable[a] (adjusted)	
Factor	**Risk Ratio**	**95% CI**	**Risk Ratio**	**95% CI**
Age, years				
<40	1	ref	1	ref
40-64	0.90	(0.75-1.09)	0.96	(0.82-1.14)
≥65	0.95	(0.77-1.16)	0.97	(0.81-1.17)
Female sex	1.01	(0.91-1.12)	1.06	(0.96-1.17)
Race				
White	1	ref	1	ref
African American	1.16	(1.04-1.30)	1.06	(0.95-1.19)
Other/unknown	1.06	(0.88-1.28)	0.97	(0.81-1.15)
LDL-C[b]				
<100 mg/dL	1	ref	1	ref
100-129 mg/dL	0.67	(0.61-0.74)	0.67	(0.60-0.75)
≥130 mg/dL	0.52	(0.47-0.57)	0.51	(0.46-0.57)
History of CHD[c]	0.87	(0.76-1.00)	0.91	(0.78,1.05)
Smoking	1.06	(0.93-1.20)	1.08	(0.96,1.22)
Area-level income, $				
≥75,000	1	ref	1	ref
60,000-<75,000	1	(0.84-1.20)	0.9	(0.76-1.06)
45,000-<60,000	0.99	(0.83-1.18)	0.94	(0.80-1.10)
30,000-<45,000	0.92	(0.75-1.12)	0.89	(0.74-1.07)
<30,000	1.03	(0.81-1.31)	0.95	(0.76-1.18)
Missing	0.99	(0.57-1.72)	1.04	(0.62-1.75)
Total number of medications dispensed[d]				
<5	1	ref	1	ref
5-9	0.99	(0.87-1.13)	0.97	(0.86-1.09)
≥10	0.90	(0.77-1.05)	0.98	(0.85-1.13)
Type of statin[d]				
Simvastatin	1	ref	1	ref
Lovastatin	1.17	(1.00-1.37)	1.06	(0.91-1.23)
Pravastatin	1.27	(1.13-1.44)	1.29	(1.13-1.47)
Other	0.91	(0.75-1.11)	1.11	(0.90-1.36)
Hospitalized between index and outcome dates	0.96	(0.79-1.17)	0.99	(0.82-1.20)
Cardiologist care	0.89	(0.78-1.01)	0.97	(0.85-1.11)
Statin dose titration	0.73	(0.60-0.89)	0.87	(0.70-1.08)
High-dose statin	1.15	(1.02-1.30)	0.99	(0.86-1.13)
Medication adherence (PDC)				
≥80%	1	ref	1	ref
50%-79%	1.30	(1.11-1.52)	1.31	(1.13-1.52)
<50%	1.89	(1.67-2.14)	1.88	(1.67-2.11)

CHD indicates coronary heart disease; KPGA, Kaiser Permanente Georgia; LDL-C, low-density lipoprotein cholesterol; PDC, proportion of days covered; ref, reference.

[a]Full multivariable adjustment includes all variables simultaneously.

[b]Most recent LDL-C measure in the 365 days prior to index.

[c]History of disease in the period 365 days prior to index date through outcome date.

[d]Medications dispensed in the period 365 days prior to index date through outcome date.