

Factors of Hyperlipidemia Medication Adherence in a Nationwide Health Plan

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Over 800,000 Americans die from cardiovascular disease (CVD) every year. Approximately 75% of fatal cardiac events are due to heart attack (acute myocardial infarction [AMI]) and stroke (cerebrovascular accident [CVA]).¹ Those who survive these events have a reduction in life expectancy of up to 15 years² and quality of life of nearly 50%.³⁻⁵ The direct and indirect societal costs attributable to CVD exceed \$475 billion annually.¹

A substantial body of clinical research supports lipid-lowering therapies (LLTs) as the primary therapeutic modality for reducing the risk of cardiovascular outcomes. Statins are the primary treatment modality and may confer lipid reductions of 10% to 60%.⁶ In the primary prevention of CVD, lipid reductions with low to medium potency statins have been shown to reduce the incidence of fatal and nonfatal cardiovascular outcomes significantly (by 30% to 40%).^{7,8} High potency statins may deliver a larger reduction in the risk of AMI and CVA (36% to 48%).⁹ Depending on patient need, statins, as well as fibric acid derivatives, bile acid sequestrants, niacin preparations, cholesterol absorption inhibitors, and free fatty acid products, can be individualized to help meet clinical, economic, and humanistic goals.⁶

There are significant clinical data demonstrating the efficacy of LLT in CVD; however, translating the benefits from clinical trials into real-world outcomes is hampered, in part, by low medication adherence. Clinical trials demonstrate that adequate medication adherence over 5 years is necessary to reduce the negative clinical outcomes associated with CVD.^{7,8} However, in clinical trials for LLT, full medication adherence is achieved through treatment oversight using clinical staff or by incorporating inclusion criteria that preselect patients on the basis of demonstrated medication adherence.¹⁰

Real-world adherence with LLT does not typically achieve the levels observed in clinical trials. In a study of 34,501 Medicaid patients, medication adherence with LLT dropped from 45% to 36% 3 months after LLT initiation and 79% to 56% 6 months after initiation.¹¹ Retrospective observational studies have found that women,^{11,12} nonwhite race, usage of a Medicaid plan (odds ratio [OR]: 1.60), and age >75 years

were associated with medication nonadherence.¹³ Clinically, patients with depression and dementia,¹³ a hospitalization in the year prior to the start of LLT,¹¹ or treatment with anxiolytics¹⁴ were associated with

Objectives: To evaluate the factors associated with nonadherence in a nationally representative sample of patients receiving lipid-lowering therapy (LLT).

Study Design: Retrospective database analysis of treatment-naïve (1 year without LLT claim) hyperlipidemia patients evidenced by a new pharmacy claim for lipid-lowering therapy.

Methods: Pharmacy and medical claims data were analyzed for currently enrolled members receiving a new LLT from 2007 to 2008. Adherence was defined as percentage of days covered (PDC) and values <80% were used to categorize nonadherent patients. Independent variables included patient demographics, pharmacy utilization, and medical conditions. Stepwise logistic regression was used to predict the odds of nonadherence. Laboratory data variables were incorporated in an exploratory sub-analysis to test the robustness of the original model.

Results: Adherence with LLT was estimated in 88,635 patients. Sixty-five percent of patients were nonadherent (mean PDC = 0.33). Compared with statins, patients treated with bile acid sequestrants were 6.75 times as likely to be nonadherent ($P < .001$). Significant ($P < .05$) predictors of nonadherence included age 45 to 55 years (ref: age >75 y) (odds ratio [OR]: 1.11); prior diabetes diagnosis (OR: 1.15); and unique pharmacies used (OR = 1.10). Significant factors reducing nonadherence include male gender (OR: 0.77); previous heart attack (OR: 0.82); prior adherent behavior (OR: 0.89); and unique physicians seen (OR: 0.97). Compared with no copayment, patients with \$5 to \$30 copayments had a significant reduction in the likelihood of nonadherence.

Conclusions: Medication adherence remains poor in patients receiving LLT. Treatment outcomes and healthcare resource use may be improved by prioritizing adherence programs in at-risk patient populations.

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In this issue

Take-Away Points / p194

www.ajmc.com

Full text and PDF

For author information and disclosures,
see end of text.



Take-Away Points

Adherence interventions may be best prioritized in populations at high risk for medication nonadherence. Compared with associated reference groups, our study suggests:

- Women, middle-aged patients, those treated with bile acid sequestrants, patients with diabetic and neurologic comorbid conditions, and those using multiple pharmacies had worse medication adherence.
- Medication adherence was improved in men; patients with documented heart attacks; those with prior medication adherence; those with more routine physician use; and patients with copayments ranging from \$5 to \$30.
- Laboratory data suggested patients furthest from serum lipid goals have the highest likelihood of medication nonadherence.

nonadherence. Treatment attributes including higher daily doses of LLT¹⁵ and medication switching reduced medication adherence.¹² Across studies, significant heterogeneity exists in the patient populations evaluated, model variables included, definitions of medication adherence, and reporting.

The purpose of this study was to study factors associated with nonadherence in a nationally representative sample of patients receiving LLT for dyslipidemia using several new factors not included in previous studies. This study described characteristics of adherent and nonadherent patients; identified factors with significant impact on nonadherence; and suggested strategies to operationalize these results.

METHODS

Data

Data for this study were derived from paid pharmacy and medical claims and serum lipid laboratory data from a commercial health plan with members in 14 states from 4 regions of the United States. Data covered January 1, 2006, to April 30, 2009. Patient inclusion criteria included: receipt of LLT (“index drug”) between May 1, 2007, and April 30, 2008; 1-year continuous eligibility before and after the date of index drug receipt (“index date”); and a 1-year period without an LLT claim prior to receipt of the index LLT. Medicare and Medicaid enrollees were excluded.

Pharmacy claims included demographic and pharmacy utilization information such as medications, costs, quantities, and days of supply. Medical claims captured *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)* codes and their respective diagnosis dates. Serum lipid values were retrieved for a sub-sample of patients for whom laboratory data were available. Data were de-identified and the study was approved by the Institutional Review Board at The University of Southern California.

Unit of Analysis

The unit of analysis was the patient’s first observed episode of LLT. Each patient’s pharmacy, medical claims, and

laboratory data (where available) were summarized into 1 patient-level claims data set with multiple summary variables based on the index date of first LLT. The index drug was the key variable from which adherence estimates were derived.

Percentage of days covered (PDC) was used to estimate medication adherence. PDC was defined as the days’ supply of LLT dispensed in the first year following the index date divided by 365 days, multiplied by 100. The days’ supply of LLT was calculated as the total amount of medication provided divided by the frequency of administration (60 tablets, dosed twice daily equals a 30-day supply). PDC offers the advantage of measuring both medication adherence and persistence,¹⁶ both of which are important aspects of disease control in dyslipidemia. From a health plan perspective, the fixed observation period (1 year) used in PDC calculations aligns with a typical member enrollment period and payer decision-making timelines. PDC <80% was used as the cutoff for nonadherence with LLT and was the primary outcome variable.

Predictors of Suboptimal Adherence

Potential predictors of nonadherence included patient demographics; dichotomous variables based on selected ICD-9-CM codes; and variables capturing pharmacy and healthcare provider utilization in the year before the receipt of the index drug. Characteristics of the index drug such as copayment level and therapeutic class were also used as predictive covariates. Prior adherent behavior was defined as the ratio of total number of prescriptions filled and refilled to the total number of unique medications used. A sub-analysis of patients with laboratory data was also performed. Evaluated here were the predictive value of baseline low-density lipoprotein (LDL) values; unique laboratory visits; and elapsed time between the most recent LDL laboratory and index date on nonadherence. This analysis was also meant to act as a sensitivity analysis to test the robustness of the full primary model.

Statistical Methods

The population was divided into adherent and nonadherent members, and descriptive statistics were compared using student *t* tests and χ^2 tests. PDC <80% was regressed on covariates derived from demographic, pharmacy, medical, and laboratory data using stepwise logistic regression. Multilevel categorical variables such as age categories were forced into the model if any 1 age category was found to be significant. Significant predictors of nonadherence were



Factors Associated With Hyperlipidemia Medication Adherence

■ **Table 1.** Descriptive Characteristics by Adherence Classification (N = 88,635)

Attribute	Percentage Days Covered >0.8 (n = 30,561)		Percentage Days Covered <0.8 (n = 58,074)		<.001
	n	%	n	%	P
Male gender	16,993	55.6	29,681	51.1	<.001
PDC, mean (SD)	1.03 (0.2)	n/a	0.33 (0.22)	n/a	<.001
Age, mean (SD)	53.7 (10.2)	n/a	51.2 (11.7)	n/a	<.001
Region					
Central	9891	32.3	17,179	29.5	<.001
East	11,638	38.0	24,811	42.7	<.001
West	8916	29.1	15,884	27.3	<.001
Therapeutic class variables					
Fibric acid derivatives	2579	8.4	4980	8.5	.4895
Niacin products	531	1.7	1560	2.6	<.001
Bile acid sequestrants	214	0.7	2849	4.9	<.001
Cholesterol absorption inhibitors	610	2.0	1143	1.9	.7773
Combination products	890	2.9	1953	3.3	.0003
Free fatty acid products	446	1.4	1796	3.0	<.001
Statins	25,291	82.7	43,793	75.4	<.001
Diagnosis categories					
Total ICD-9-CM codes, mean (SD)	6.7 (7.0)	n/a	7.3 (7.7)	n/a	<.001
Stroke	457	1.5	929	1.6	.2341
Hypertension	10,786	35.2	19,409	33.4	<.001
Atherosclerotic disease	1690	5.5	3391	5.8	.0598
Diabetes mellitus	3803	12.4	7811	13.4	<.001
Neurological diseases	3833	12.5	8384	14.4	<.001
Acute myocardial infarction	252	0.8	428	0.7	.1555
Coronary heart disease	610	2.00	1315	2.2	.0092
Dyslipidemia diagnosis	11,040	36.1	20,650	35.5	.0945
Other diseases	2986	9.77	6069	10.45	.0015
Laboratory (LDL) data sub-analysis (n = 16,400)					
	n = 5342		n = 11,058		<.001
Unique laboratory visits, mean (SD)	2.0 (1.2)	n/a	1.9 (1.2)	n/a	<.001
Recent laboratory/index medication gap, mean (SD)	12.8 (9.5)	n/a	12 (9.3)	n/a	<.001
Baseline LDL (mg/dL), mean (SD)	140.6 (40.0)	n/a	144.5 (39.5)	n/a	<.001

ICD-9-CM indicates *International Classification of Diseases, Ninth Revision, Clinical Modification*; LDL, low-density lipoprotein; n/a, not applicable; SD, standard deviation.

identified at the $P < .05$ level. All statistical analyses were performed using SAS version 9.1 (SAS Institute Inc, Cary, North Carolina).

RESULTS

Descriptive Statistics

Descriptive statistics can be found in **Table 1**. In total, 88,635 patients were identified and 65% (n = 58,074) were

nonadherent with LLT over the first posttreatment year. Mean PDC was significantly ($P < .05$) lower in nonadherent versus adherent patients (PDC = 33% vs 100%). Adherent patients were significantly older (53.7 vs 51.2 years) and male (55.6% vs 51.1%) compared with nonadherent patients. The number of comorbid conditions recorded in nonadherent patients was significantly greater than in adherent patients. Statins were the most commonly initiated treatment, and utilization was significantly higher in adherent patients. Where available,

■ **Table 2.** Potential Predictors and Their Association With Nonadherence

Demographics				
Variable	Odds Ratio	Lower Limit	Upper Limit	P
Male gender	0.77	0.747	0.794	<.001
Central region ^a	1.058	1.017	1.101	.0054
East region ^a	1.164	1.122	1.207	<.001
Age (reference: age <25), y				
25 to 35	0.741	0.582	0.943	.0147
35 to 45	0.519	0.412	0.653	<.001
45 to 55	0.374	0.297	0.47	<.001
55 to 65	0.304	0.242	0.382	<.001
65 to 75	0.346	0.273	0.438	<.001
>75	0.337	0.264	0.429	<.001
Index copayment (reference: index copayment = \$0)				
Index copay: \$0 to ≤\$5	0.946	0.884	1.013	.1116
Index copay: \$6 to ≤\$10	0.877	0.836	0.92	<.001
Index copay: \$11 to ≤\$20	0.879	0.837	0.923	<.001
Index copay: \$21 to ≤\$30	0.939	0.894	0.987	.0128
Index copay: >\$30	0.991	0.939	1.046	.7409
Mail order utilization ^b	0.442	0.422	0.463	<.001
Previous medication adherence	0.888	0.882	0.894	<.001
Unique medications	1	0.996	1.005	.938
Unique physicians	0.969	0.958	0.98	<.001
Unique pharmacies	1.102	1.083	1.122	<.001
Drug classes (reference: statins)				
Absorption inhibitors	1.173	1.058	1.3	.0024
Combination products	1.204	1.104	1.313	<.001
Free fatty acid products	2.257	2.026	2.516	<.001
Fibric acid derivatives	1.051	0.997	1.108	.0642
Niacin products	1.744	1.573	1.934	<.001
Bile acid sequestrants	6.766	5.868	7.802	<.001
Diagnosis categories (reference: no specified diagnosis)				
Total ICD-9-CM codes captured	1.005	1.002	1.008	.0002
Acute myocardial infarction	0.821	0.693	0.972	.0222
Atherosclerotic disease	1.094	1.019	1.176	.0137
Coronary heart disease	1.076	0.967	1.197	.1781
Diabetes mellitus	1.153	1.102	1.207	<.001
Hypertension	1.016	0.981	1.052	.3859
Neurological diseases	1.096	1.048	1.147	<.001
Other diseases	1.104	1.049	1.161	.0002

ICD-9-CM indicates *International Classification of Diseases, Ninth Revision, Clinical Modification*.

^aReference = western region.

^bReference = no mail order utilization.

baseline LDL values were significantly higher for nonadherent patients (144.5 vs 140.6 mg/dL).

Predictors of Nonadherence

The results of the stepwise regression of the predictors of nonadherence with LLT are displayed in **Table 2**. This proce-

dure resulted in 34 predictors of nonadherence with differential levels of significance.

Drug Class: There were 36 drug products used to initiate treatment for dyslipidemia which were further grouped into therapeutic class variables. Patients using bile acid sequestrants were 6.7 times as likely to be nonadherent as patients treated



■ **Table 3.** Laboratory Data Sensitivity Analysis and Laboratory Data Predictors of Nonadherence

Variable	Full Model	Laboratory Data Sensitivity Analysis	
	Odds Ratio	Odds Ratio	Percent Change
Nonsignificant to significant			
Fibric acid derivatives	1.051	1.292 ^a	22.9%
Hypertension	1.016	1.101 ^b	8.4%
Index copay: >\$30	0.991	0.844 ^b	14.8%
Significant to nonsignificant			
Cholesterol absorption inhibitors	1.173 ^a	1.318	12.4%
Age 25 to 35 y	0.741 ^b	1.019	37.5%
Age 35 to 45 y	0.519 ^c	0.717	38.2%
Age >75 y	0.337 ^c	0.521	54.6%
Atherosclerotic disease	1.094 ^b	1.15	5.1%
Central region	1.058 ^a	0.978	7.6%
Combination products	1.204 ^c	1.26	4.7%
Total ICD-9-CM codes	1.005 ^a	1.006	0.1%
Laboratory data variables			
Variable	Reference	Odds Ratio	95% CI
Unique laboratory visits	n/a	0.966 ^b	0.938-0.995
Recent laboratory/index medication gap	n/a	0.994 ^a	0.990-0.997
Baseline LDL value categories			
100 to ≤130 mg/dL	<100 mg/dL	1.076	0.956-1.211
131 to ≤145 mg/dL	<100 mg/dL	1.22 ^a	1.075-1.386
146 to ≤160 mg/dL	<100 mg/dL	1.218 ^a	1.074-1.38
161 to ≤180 mg/dL	<100 mg/dL	1.205 ^a	1.063-1.366
>180 mg/dL	<100 mg/dL	1.323 ^c	1.161-1.508

CI indicates confidence interval; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; LDL, low-density lipoprotein.
^a<0.01.
^b<0.05.
^c<0.001.

with statins (95% confidence interval [CI]: 5.8-7.8). Patients using niacin products, free fatty acid products, cholesterol absorption inhibitors, and combination products were all significantly more likely to be nonadherent ($P \leq .002$). The impact of treatment with fibrates on nonadherence was nonsignificant.

Index Copayment: Compared with patients having a \$0 copayment, patients with copayments of \$5 to \$10, \$10 to \$20, and \$20 to \$30 (taken together, \$5 to \$30) had a significantly decreased likelihood of nonadherence of 12%, 12%, and 6%, respectively (all $P < .01$). Copayment levels of \$0 to \$5 and greater than \$30 also decreased nonadherence, but these effects were nonsignificant.

Age, Sex, Region: A significant gender effect was found: male patients were 23% less likely to be nonadherent versus females ($P < .001$). Increasing age was found to decrease nonadherence. Patients aged 25 to 35 years were 26% less likely to be nonadherent versus those under 25 years of age. Patients over 75 years of age were 67% less likely to be nonadherent

than the youngest patients. Patients located in the Central and East regions had roughly a 6% and 16% increased likelihood of nonadherence versus those in the West region, respectively ($P < .005$).

Health Care Practitioner Utilization: Patients who visited more physicians had a significantly decreased risk of nonadherence ($P < .001$). In contrast, each additional pharmacy used to dispense prescriptions in the pre-period increased the risk of nonadherence by 10% ($P < .001$).

Comorbidity Profile: Patients experiencing an AMI were 18% less likely to be nonadherent ($P < .02$). Patients with atherosclerotic diseases and patients with neurological disorders were both found to be 10% more likely to be nonadherent ($P < .01$). Further, patients with diabetes had a 15% higher likelihood of nonadherence versus those without diabetes ($P < .001$). A diagnosis of hypertension or coronary heart disease had no significant impact on the likelihood of complying with medications for dyslipidemia.



Prior Adherent Behavior: An increase in the number of refills per medication used in the pre-period (better theoretical adherence) reduced the likelihood of nonadherence by 12% ($P < .001$) per unit increase in this ratio. While this proxy measure of prior adherence behavior met criteria for inclusion into the model, its components did not. Total prescriptions filled and total unique medications used did not meet the $P < .05$ level of significance.

Laboratory Data Sub-Analysis

Table 3 presents the results from the sub-analysis of nonadherence in patients with laboratory data ($n = 16,400$).

Baseline LDL: As described in the methods, the baseline, pre-treatment LDL value (LDL value recorded on or before LLT initiation) was used as a potential predictor of medication adherence. In general, patients with higher baseline LDL values had an increased likelihood of nonadherence. Elevated baseline LDL increased the likelihood of nonadherence significantly, by 20% to 22% ($P \leq .003$) across all LDL level categories, compared with those patients already at goal (LDL < 100 mg/dL). Patients with baseline LDL greater than 180 mg/dL were found to have 32% increased probability of nonadherence versus patients at goal ($P < .001$).

Time Between Tests and Treatment: The absolute value of the time between most recent LDL laboratory test and index date was also found to have an influence on a patient's likelihood of nonadherence. Each additional day between the final laboratory and index date decreased the likelihood of nonadherence by 0.006% ($P = .0006$).

Unique Laboratory Tests: The variable was estimated based on all the laboratories received for each patient, in addition to LDL, in the year prior to initiating drug therapy. It was found that each unique laboratory "visit" decreased the probability of nonadherence by 3.4% ($P = .02$).

Sensitivity of Results From the Primary Model to Laboratory Data Inclusion: In the laboratory data model, significant parameter estimates from the full model became nonsignificant. This was likely due to the significant reduction in sample size in the sub-analysis, as none of these changes affected the direction or magnitude of the estimated effect. In contrast, some nonsignificant predictors in the full model became significant in the laboratory data sub-analysis. Compared with those initiating treatment with statins, patients treated with fibric acid products were 29% more likely to be nonadherent ($P = .0003$). Similarly, a hypertension diagnosis (vs no hypertension diagnosis) in the sub-analysis was found to increase the probability of nonadherence significantly, by 10% ($P = .02$). Lastly, index copayments over \$30 decreased nonadherence by 16% ($P = .01$) compared with \$0 index copayment. The association and direction of other copayment levels on adherence was unchanged in

the sub-analysis (eg, \$0 to \$5, \$5 to \$10, \$10 to \$20, and \$20 to \$30). Although nonsignificant in the full model, the direction of effect of fibric acid index prescription, hypertension diagnosis, and index copayment $> \$30$ on nonadherence was not influenced by the addition of laboratory data.

DISCUSSION

The purpose of this study was to evaluate the factors associated with nonadherence in a nationally representative sample of patients receiving LLT for dyslipidemia. To meet this objective, 88,635 patients naïve to LLT were captured from commercial health plans across the United States and predictive models regressing nonadherence with LLT on demographic, clinical, and treatment characteristics were developed from pharmacy and medical data. The addition of laboratory data covariates were used to construct an exploratory analysis investigating the effect of laboratory data on the sensitivity of the covariates identified in the primary analysis.

The results from this study raise interesting questions regarding patient- and healthcare-level factors associated with medication nonadherence. The large and significant increase in nonadherence with bile acid sequestrants draws an expected link between low adherence, frequent daily dosing, and a troublesome side effect profile. An increase in nonadherence in those using more unique pharmacies suggests that pharmacy benefit managers may reduce nonadherence by identifying and reducing polypharmacy. Previous studies have reported that higher pharmacy copayments are associated with reductions in medication adherence; however, the present study found that modest copayments (compared with no copayment) did not adversely affect medication adherence after controlling for baseline demographic and clinical characteristics. Other data that may help explain these findings, such as formulary tier placement and copayment amounts for alternatives, were not available. Future adherence research evaluating the influence of formulary design and cost-sharing structure would help clarify our understanding of how patient out-of-pocket costs impact medication adherence.

The study reported interesting connections between a patient's clinical profile and medication nonadherence. The reduced risk of nonadherence in patients seeing their physician more often can be interpreted as a blend of both patient behaviors and physician support helping to improve medication adherence outcomes. Tangible, negative health outcomes, such as an AMI, may improve medication adherence, while the opposite is true for less pronounced conditions such as atherosclerosis or diabetes. Although exploratory, we found that disease severity as measured by the distance from LDL goal increased the likelihood of nonadherence. This may indicate that initial

Factors Associated With Hyperlipidemia Medication Adherence

laboratory values are both a measurement of disease severity and a proxy for poor adherence with therapeutic lifestyle modifications. Intuitively, as baseline LDL values increase, so does the need to proactively address medication adherence.

Some results from this study share similar themes with the primary literature, yet other results contrast with previous studies. Results agreeing with previous research include reduced nonadherence in those with prior AMI^{17,18} and increased nonadherence in women and those with neurological disease.^{11,15} Other studies showed that gender had no effect on nonadherence; older age was shown to increase nonadherence; diabetes had a nonsignificant effect on nonadherence; and the use of additional unique physicians was not shown to significantly impact nonadherence; all of which disagreed with this study.^{11,17,18}

As with all studies, there are limitations to consider upon interpretation. First, Medicare and Medicaid recipients were excluded from this analysis, which may have introduced selection bias. Methodologically, PDC as a proxy for medication adherence is acceptable; however, the effect of using alternative adherence definitions on study outcomes was not evaluated. As with any retrospective analysis, the relationship between covariates and nonadherence cannot be interpreted as causal, as the association may be confounded by latent or unmeasured variables.

There are potential applications for this research in commercial health plans. These results may help target adherence interventions in patient populations such as females with neurological diseases, new to LLT. With increased utilization of electronic medical records, predictive models may help develop real-time, nonadherence risk scores and may proactively initiate conversations about medication adherence. Pharmacoeconomic models for LLT in new-start patients can utilize the reported odds ratios in product assessments of budget impact or cost-effectiveness to adjust the proportion of patients remaining on LLT at the end of 1 year. Across applications, medication adherence research may be used to more efficiently allocate healthcare resources by targeting drug budgets and prioritizing adherence programs in at-risk patient populations.

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