

# Determinants of Compliance With Statin Therapy and Low-Density Lipoprotein Cholesterol Goal Attainment in a Managed Care Population

Jennifer S. Schultz, PhD; John C. O'Donnell, PhD; Ken L. McDonough, MD; Rahul Sasane, PhD; and Jay Meyer, PhD

**Objective:** To identify determinants of medication compliance and low-density lipoprotein cholesterol goal attainment.

**Study Design:** This retrospective analysis used claims data from a large, national, employment-based independent practice association database. Subjects were identified based on the existence of a filled prescription for statin therapy between April 1, 1999, and June 30, 2001. Subjects had to be 18 years or older, continuously enrolled in the health plan for 2 years, and new users of statin therapy.

**Methods:** Multivariate logistic regression models were used to identify predictors of compliance and goal attainment in high-risk subjects.

**Results:** As the mean copayment for statins increased, there was a decrease in the likelihood of compliance. Of the subjects with laboratory results, 50.7% attained their low-density lipoprotein cholesterol goal level established by National Cholesterol Education Program Adult Treatment Panel III guidelines. Older individuals and men were more likely to reach their low-density lipoprotein cholesterol target goal, as were individuals who were compliant with their statin therapy.

**Conclusions:** Compliance with statin therapy in the managed care setting remains poor. Of particular concern is the lower level of compliance among women and younger high-risk patients, along with patients who have fewer outpatient visits associated with hyperlipidemia and lower incidences of cholesterol testing.

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Coronary heart disease (CHD) is the single leading cause of death in the United States, with more than 650 000 mortalities from CHD-related causes each year.<sup>1</sup> Dyslipidemia is acknowledged as a major risk factor for CHD. A large body of evidence from epidemiological studies<sup>2-5</sup> suggests that lower low-density lipoprotein cholesterol (LDL-C) levels are associated with lower overall risk of CHD morbidity and mortality. Clinical trials have shown that 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) can significantly lower cholesterol levels and reduce CHD-related morbidity and mortality.<sup>6,7</sup> However, several studies<sup>8-10</sup> have demonstrated less than optimal levels of compliance and persistence with statin regimens in various patient populations, including older persons, managed care enrollees, Medicaid enrollees, and patients with acute coronary syndrome.

Several studies have attempted to identify correlates of patient noncompliance with statin therapy. Patient copayment level, the number of medications taken concurrently, and the days supplied per prescription were found to be significantly associated with compliance with statin therapy.<sup>11</sup> Increased number of comorbidities has also been found to be associated with increased compliance with statin therapy,<sup>8,10</sup> as has membership in a primary prevention cohort as opposed to a secondary prevention cohort.<sup>9,12</sup> Increased age, however, has been associated with decreased compliance.<sup>10</sup> Maviglia et al<sup>12</sup> identified a relationship between patients' LDL-C levels and their compliance with statin therapy. These authors report that subjects who were noncompliant with their statin therapy were least likely to have had their LDL-C levels checked.

To increase compliance rates among statin users, it is crucial to focus interventions that are geared toward increasing adherence to statin regimens on patients who are likely to be noncompliant with therapy. This study examines predictors of patient compliance with statin therapy and attainment of LDL-C goal levels using a large retrospective longitudinal administrative claims database. Using claims data provides a real-world depiction of medication use in terms of the frequency and regularity in which prescriptions are refilled by patients and their ability to attain LDL-C goal levels.

## METHODS

### Study Population

This study used retrospective longitudinal claims data from 23 fee-for-service independent practice association health plans affiliated with a large, national man-

From the Department of Economics, University of Minnesota, Duluth (JSS); AstraZeneca LP, Wilmington, Del (JCO, KLM, RS); and Ingenix Inc, Eden Prairie, Minn (JM). Funding for this study was provided by AstraZeneca LP.

Address correspondence to: Jennifer S. Schultz, PhD, Department of Economics, University of Minnesota, 165 SBE, 412 Library Drive, Duluth, MN 55812. E-mail: jschultz@d.umn.edu.

## Compliance With Statin Therapy

aged care organization. These health plans are located in various states throughout the western, midwestern, southern, southeastern, and northeastern United States, providing coverage for inpatient care, ambulatory services, and prescription drugs. The study sample was selected from the population of commercially insured health plan members 18 years of age or older who had pharmacy benefits and who were continuously enrolled in the health plan for 2 years. Patients with newly filled prescriptions for statins were identified from April 1, 1999, through June 30, 2001 (the index date was the date of the first filled statin prescription for each patient), and medical and pharmacy claims from April 1, 1998, through June 30, 2002, were used to capture 2 years of data for each patient (12 months before the index date and 12 months after the index date). Patients at high risk for CHD or CHD equivalents, as established by the National Cholesterol Education Program Adult Treatment Panel III guidelines,<sup>13</sup> were identified using *International Classification of Diseases, Ninth Revision, Clinical Modification*

(*ICD-9-CM*) diagnostic codes; 2002 *Current Procedural Terminology (CPT)* procedural codes; or filled prescriptions in medical and pharmacy claims (**Table 1**). Medical, pharmacy, and laboratory claims data were used to characterize health status, healthcare use, hyperlipidemia treatment patterns, and LDL-C levels.<sup>13</sup>

### Data Measures

Data on variables related to statin therapy, compliance, and goal attainment were gathered from the medical claims database; these included demographic information, health conditions, and healthcare resource use. Information on demographic variables, including sex and age, was obtained from enrollment files.

Information regarding comorbid conditions present during the study was obtained from the medical and pharmacy claims database using *ICD-9-CM* codes, *CPT* codes, and prescription drug fills (**Table 2**). Drug use and prescription fill dates were obtained from the pharmacy claims database using national drug codes. Healthcare use during the baseline period—including measures of

**Table 1.** Factors Used to Determine Risk of Coronary Heart Disease (CHD) or CHD Equivalents

Risk Factor	ICD-9-CM Code	CPT Code	Filled Prescription Drug
Acute myocardial infarction	410.xx	—	—
Other acute and subacute forms of ischemic heart disease	411.xx	—	—
Old myocardial infarction	412.xx	—	—
Angina pectoris	413.xx	—	Nitrates
Other forms of chronic ischemic heart disease	414.xx	—	—
Atherosclerosis	429.2, 437.0, 437.1, 440.xx Procedure codes: 36.0x-36.3x, 38.12-38.14, 38.16, 38.18, 38.34, 38.44, 39.22-39.26, 39.28, 39.29, 39.50, 99.10	35301, 35311-35381, 35390, 33510-33536, 35450-35495, 33572, 35500-35683, 92975-92977, 92980-92981, 92982-92984, 92995-92996	—
Stroke	433.xx, 434.0x, 434.9x, 435.x, 436.xx	—	Antiplatelets
Peripheral vascular disease	441.xx, 443.xx	33877, 34800-34832, 35081-35103	Pentoxifylline
Diabetes mellitus	250.xx, 362.0x, 366.41	—	Insulin, oral hypoglycemic drugs

*CPT* indicates *Current Procedural Terminology*; *ICD-9-CM*, *International Classification of Diseases, Ninth Revision, Clinical Modification*.

## CLINICAL

ambulatory visits associated with hyperlipidemia (defined using *ICD-9-CM* codes 272.0x-272.2x, 272.4x, or 272.9x), any visits to an emergency department, any inpatient hospital visits, any cardiovascular procedures (defined using *CPT* codes 33503-33506, 33510-33516, 33517-33530, 33536, 92980, 92982, 92984, 92997, or 92998 or *ICD-9-CM* procedure codes 36.00-36.03, 36.05, or 36.09), and any diagnoses of ischemic heart disease (defined using *ICD-9-CM* codes 410.xx-414.xx or prescription fills for nitrates)—was measured using medical and pharmacy claims data. The number of cholesterol tests conducted in the baseline period was identified in medical claims using the following *CPT* codes: 80061, 82465, 83715, 83716, and 83721. Healthcare use in the baseline period and baseline healthcare costs were used as measures of health and disease severity.

The mean statin prescription copayment was calculated using pharmacy claims data for all patients during the 12-month follow-up. The ratio of the number of filled statin prescriptions by mail order to the number filled by retail pharmacies was constructed for the follow-up period using pharmacy claims data.

Pharmacy claims data were used to determine patterns of statin therapy during the study. Information was extracted regarding the number of filled prescriptions and days' supply of filled prescriptions for statin medications during follow-up. An adherence ratio was calculated to measure compliance by dividing the total days' supply of statins by the length of possible treatment (365 days). Compliance was defined as an adherence ratio of at least 80% or a daily dose of medication available for at least 80% of the days in the period.<sup>14</sup> The ratio incorporates a measure of persistency as well

**Table 2.** Information Used To Identify Comorbid Conditions

Comorbidity	ICD-9-CM Code	Filled Prescription Drug
Alcohol or drug abuse	303.xx, 304.xx, 305.xx, V11.3	—
Stroke	433.xx-436.xx	—
Diabetes mellitus	250.xx, 362.0x, 366.41	Insulin or oral hypoglycemics
Cancer	140.xx-208.xx, 230.xx-234.xx	—
Benign neoplasm	209.xx-229.xx, 235.xx-239.xx	—
Arthritis	714.xx, 715.xx	—
Hypertension	401.xx, 362.11, 402.xx, 403.xx, 404.xx, 437.2	Angiotensin-converting enzyme inhibitors, angiotensin modifying agents, angiotensin II receptor antagonists, centrally acting antihypertensives, diuretics, vasodilator antihypertensives
Renal failure	584.xx-586.xx	—
Obesity	278.0x	—
Ischemic heart disease	410.xx-414.xx	Nitrates
Atherosclerosis	429.2, 437.0, 437.1, 440.xx Procedure codes: 36.0x-36.3x, 38.12-38.14, 38.16, 38.18, 38.34, 38.44, 39.22-39.26, 39.28, 39.29, 39.50, 99.10 CPT codes: 33510-33536, 33572, 92975-92977, 92980-92981, 92982-92984, 92995-92996	—
Depression or other affective disorders and anxiety disorders	296.xx, 306.2, 300.xx	Anxiolytics, antidepressants, selective serotonin reuptake inhibitors, tricyclics, antipsychotic drugs, sedative hypnotics
Osteoporosis	733.0x	—

*CPT* indicates Current Procedural Terminology; *ICD-9-CM*, International Classification of Diseases, Ninth Revision, Clinical Modification.

because it includes all statin users, including those with a single filled prescription.

## RESULTS

### Descriptive Analysis

A total of 21 239 new statin users were identified as being at high risk for CHD and met all the inclusion criteria for the analysis. **Table 3** provides descriptive characteristics, as well as statistical analyses of means and proportions, for the compliant and noncompliant cohorts.

### Statistical Analysis

**Compliance With Statin Therapy.** A logistic regression model was used to determine the predictors of compliance with statin therapy in the first 365 days of treatment after the index date. Covariates in the model included age, sex, number of comorbidities, presence of ischemic heart disease, number of hyperlipidemia ambulatory visits, number of cholesterol tests, occurrence of a cardiovascular procedure, occurrence of an inpatient hospitalization, any visits to an emergency department, total healthcare costs, the mean statin copayment, and the ratio of filled statin prescriptions via mail order vs retail store. Predictors were selected based on information from the medical literature regarding compliance with medications and hypothesized relationships between the covariates and compliance.<sup>8-12,15,16</sup>

According to the results of the multiple logistic regression analysis for high-risk patients, older subjects and men were significantly more compliant with statin therapy, as were patients with more baseline outpatient visits associated with hyperlipidemia (**Table 4**). Patients with an occurrence of a cardiovascular procedure or inpatient hospitalization during the baseline period were more compliant with statin therapy. However, patients who had at least 1 visit to an emergency department during the baseline period were less likely to be compliant with

statin therapy than patients with no visits. Patients who had filled their statin prescriptions via mail order were more likely to be compliant with therapy compared with those who filled more of their statin prescriptions at retail pharmacy stores. Furthermore, as the mean copayment for statins increased, there was a decrease in the likelihood of compliance.

**Attainment of Low-Density Lipoprotein Cholesterol Goal.** A model of goal attainment was developed to determine whether compliance with statin therapy was associated with health outcomes after controlling for other covariates. Approximately 4219 individuals from the entire cohort had at least 1 LDL-C laboratory result from the 60 days after the index date to the end of the study. The subcohort with LDL-C results is similar to the larger cohort in terms of age, sex, compliance, baseline costs, and health status measures. Of these, 2141 (50.7%) attained their LDL-C goal level, according to National Cholesterol Education Program Adult Treatment Panel III guidelines,<sup>13</sup> during the relevant period. The mean  $\pm$  SD LDL-C laboratory value for those who attained their goal level was  $80 \pm 15$  mg/dL

**Table 3.** Summary of Demographic and Descriptive Characteristics During the 12-month Baseline Period\*

Characteristic	Compliant Cohort (n = 9066)	Noncompliant Cohort (n = 12 173)	P
<b>Demographics</b>			
Male	6129 (67.6) <sup>†</sup>	7088 (58.2)	< .001
Age, y	55.32 $\pm$ 8.84 <sup>‡</sup>	53.00 $\pm$ 9.52	< .001
<b>Health status</b>			
Comorbidities	3.01 $\pm$ 1.43 <sup>‡</sup>	2.73 $\pm$ 1.43	< .001
Ischemic heart disease	4980 (54.9) <sup>†</sup>	5548 (45.6)	< .001
<b>Healthcare use</b>			
Outpatient hyperlipidemia visits	1.29 $\pm$ 1.64 <sup>‡</sup>	1.07 $\pm$ 1.53	< .001
Cholesterol tests	1.62 $\pm$ 1.45 <sup>‡</sup>	1.45 $\pm$ 1.38	< .001
Cardiovascular procedures	1941 (21.4) <sup>†</sup>	1312 (10.8)	< .001
Hospitalizations	3111 (34.3) <sup>†</sup>	3055 (25.1)	< .001
Emergency department visits	3264 (36.0) <sup>†</sup>	4090 (35.6)	< .001
Healthcare costs	9187 $\pm$ 14 112 <sup>‡</sup>	6772 $\pm$ 12 124	< .001
Mail to retail statin fills ratio	0.21 $\pm$ 0.85 <sup>‡</sup>	0.04 $\pm$ 0.30	< .001
Statin copayment, \$	15.46 $\pm$ 8.18	15.45 $\pm$ 7.52	.95

\*Data are given as number (percentage) or as means  $\pm$  SDs, unless otherwise indicated.

<sup>†</sup>Statistically significant difference based on Cochran-Mantel-Haenszel test.

<sup>‡</sup>Statistically significant difference based on *t* test.

**Table 4.** Compliance During the Follow-up Period Among the Entire Cohort of 21 239

Variable	Parameter Estimate	Odds Ratio (95% Wald Confidence Limits)
Intercept	-2.17	—
Age	0.03	1.03 (1.02-1.03)
Male	0.35	1.42 (1.33-1.50)
Baseline healthcare costs	0.003	1.003 (1.000-1.006)
Comorbidity index	0.02	1.02 (1.00-1.05)
Cholesterol tests	0.08	1.08 (1.06-1.11)
Outpatient hyperlipidemia visits	0.06	1.07 (1.04-1.09)
Emergency department visits	-0.13	0.88 (0.82-0.95)
Hospitalizations	0.12	1.13 (1.03-1.24)
Ischemic heart disease	0.03	1.03 (0.97-1.10)
Cardiovascular procedures	0.68	1.97 (1.78-2.19)
Statin copayment	-0.01	0.99 (0.98-0.99)
Mail to retail statin fills ratio	0.61	1.83 (1.71-1.97)

**Table 5.** Attainment of Low-Density Lipoprotein Cholesterol (LDL-C) Goal During the Follow-up Period Among the Subcohort of 4219 Patients With Baseline LDL-C Results

Variable	Parameter Estimate	Odds Ratio (95% Wald Confidence Limits)
Intercept	-2.63	—
Age	0.01	1.01 (1.00-1.02)
Male	0.24	1.27 (1.12-1.46)
Baseline healthcare costs	0.008	1.01 (1.00-1.02)
Comorbidity index	0.07	1.07 (1.01-1.13)
Cholesterol tests	0.10	1.10 (1.05-1.16)
Outpatient hyperlipidemia visits	-0.002	0.998 (0.956-1.042)
Emergency department visits	-0.02	0.98 (0.84-1.15)
Hospitalizations	-0.16	0.85 (0.69-1.06)
Ischemic heart disease	0.08	1.08 (0.93-1.25)
Cardiovascular procedures	0.41	1.50 (1.18-1.92)
Statin copayment	0.001	1.001 (0.992-1.010)
Mail to retail statin fills ratio	0.12	1.13 (1.02-1.25)
Compliance during 90 d	1.62	5.07 (3.92-6.55)

(2.07 ± 0.39 mmol/L). The mean ± SD number of days to attain the LDL-C goal level after initiation of statin therapy was 189 ± 90 days. A mean ± SD of 5 ± 3 statin prescriptions were filled before attainment of the LDL-C goal level, with a mean ± SD days' supply of 34.75 ± 14.68 days.

Maximum likelihood estimation was used to predict whether individuals with laboratory results attained their LDL-C goal level. A logistic regression model was used with a dichotomous dependent variable representing whether individuals attained their LDL-C goal within at least 60 days after their index date. The results (Table 5) suggest that older individuals at high risk for CHD were more likely to attain their LDL-C goal level compared with younger individuals (adding 10 years results in a 12.7% higher odds of attaining their goal). Men had a 27.4% higher odds of attaining their goal compared with women. Individuals with more baseline comorbidities had a 6.8% higher odds of attaining their goal. Individuals with 2 additional cholesterol tests had a 22.1% higher odds of attaining their goal. Individuals who underwent a cardiovascular procedure during the baseline period had a 50.4% higher odds of attaining their goal. Individuals with a higher proportion of their statin prescriptions filled via mail order had a higher odds of attaining their goal. Finally, individuals who were compliant with statin therapy in the first 90 days had a 5 times higher odds of attaining their goal compared with individuals who were not compliant.

A second logistic regression model was estimated using a subcohort of 1464 patients with LDL-C laboratory results in the follow-up period, in addition to baseline LDL-C test results. The results from this model (Table 6) suggest that individuals with higher baseline LDL-C values were less likely to attain their LDL-C goal level.

DISCUSSION

The objective of this study was to identify predictors of compliance with statin therapy and LDL-C goal attainment among patients at high risk for CHD. This

study demonstrated that, among high-risk users of statin therapy, younger subjects and women were significantly less compliant with statin therapy, as were patients with fewer baseline outpatient visits associated with hyperlipidemia. The mean statin copayment had a large effect on compliance. If the mean copayment increases by \$15, the probability of compliance decreases by 10 percentage points; if it increases by \$50, the probability of compliance decreases by 34 percentage points. High-risk patients were less likely to attain their LDL-C goal if they were younger, were female, were noncompliant with statin therapy, or had higher baseline LDL-C results. Intervention programs should target these patients to improve their health outcomes.

There are several limitations when using secondary administrative health-care claims data. First, the study results may not be generalizable to the entire US population, as the data source consisted of employer-based managed care enrollees. However, the results can be generalized to other employer-based health plans with enrollees of similar age and diagnosis. Second, an adherence ratio was used as a proxy for compliance. These ratios may significantly underestimate compliance because of different factors that may prolong the supply of medication; these include but are not limited to changes in prescription by a physician, hospitalization, or provision of medication samples. On the other hand, they may overestimate compliance if patients fill their prescriptions but do not take them.

Despite the limitations of retrospective claims data, the present study allowed for evaluation of predictors of compliance with statin therapy in a real-life setting. Clinical trials of statin therapy often exclude patients with comorbidities and generally are not representative of all patients who subsequently receive treatment. The data for the present study came from diverse regions of the country and thus may be considered representative of health plan enrollees from various geographic areas in the United States. In addition, the claims data examined are current and likely representative of current patterns of care.

CONCLUSIONS

The results indicate that compliance with statin therapy in the managed care setting remains poor. Of

**Table 6.** Attainment of Low-Density Lipoprotein Cholesterol (LDL-C) Goal During the Follow-up Period Among the Subcohort of 1464 Patients With Baseline and Follow-up LDL-C Results

Variable	Parameter Estimate	Odds Ratio (95% Wald Confidence Limits)
Intercept	0.40	—
Age	0.02	1.02 (1.01-1.04)
Male	0.25	1.29 (1.01-1.63)
Baseline healthcare costs	-0.002	0.998 (0.981-1.016)
Comorbidity index	0.05	1.05 (0.95-1.16)
Cholesterol tests	0.11	1.11 (1.00-1.23)
Outpatient hyperlipidemia visits	-0.04	0.96 (0.89-1.04)
Emergency department visits	0.06	1.06 (0.80-1.41)
Hospitalizations	-0.22	0.80 (0.53-1.22)
Ischemic heart disease	-0.02	0.98 (0.75-1.27)
Cardiovascular procedures	0.20	1.22 (0.73-2.05)
Statin copayment	-0.007	0.993 (0.976-1.009)
Mail to retail statin fills ratio	0.14	1.16 (0.96-1.39)
Compliance during 90 d	1.65	5.18 (3.29-8.17)
Baseline LDL-C value	-0.02	0.98 (0.98-0.98)

particular concern is the lower level of compliance among female and younger high-risk patients, along with patients who have fewer outpatient visits associated with hyperlipidemia and lower incidences of cholesterol testing. Together, these results suggest that managed care intervention programs would benefit patients by targeting services toward groups at risk of lower compliance, while at the same time increasing provider contact related to dyslipidemia and the availability of cholesterol testing. Intervention programs could consist of initiating information campaigns to providers, establishing and enforcing guidelines for cholesterol testing, monitoring the volume of physician contact with patients who are not filling their statin medications, sending out reminder cards to targeted patients for physician checkups, offering patient incentives to increase use of mail order statin prescriptions, and providing incentives for lowering LDL-C levels. Managed care providers interested in improving compliance might also consider addressing the barriers imposed by higher copayment costs.

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