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An Evaluation of the Factors Associated with Statin Dose Management and Low-Density Lipoprotein-Cholesterol Goal Attainment

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Abstract

Purpose: To examine factors associated with HMG-CoA reductase inhibitor (statin) management and the effect of therapeutic modifications on patients' abilities to reach their low-density lipoprotein-cholesterol (LDL-C) goal in a sample of managed care enrollees.

Methods: This retrospective analysis utilized electronic pharmacy claims, medical claims, and laboratory data, and explored the occurrence and magnitude of modifications to statin regimens. Patients aged ≥18 years who were initiated on statin therapy between 1 January 2001 and 31 December 2001 and who were continuously enrolled for 6 months prior to and 12 months following the index prescription were included. A subgroup analysis incorporated laboratory data to determine whether patients attained their LDL-C treatment goal.

Results: A total of 38 567 patients were identified: 50.6% were female and patients had a mean age of 63.6 ± 13.4 years. During a 1-year follow-up, 16.1% (n = 6220) had a modification to their statin regimen. Multivariate analysis showed that significant predictors of regimen modification included age, sex, index statin, index statin potency, and the occurrence of a cardiac reperfusion procedure or acute hospitalization during the 6-month pre-index period ($p < 0.05$). A subgroup of 254 patients with laboratory data was identified: 57.9% of these patients were female and their mean age was 66.6 ± 10.5 years. Of this cohort, only 14.2% had a modification to their statin regimen. Goal attainment was significantly more frequent among patients whose statin regimen was modified compared with patients whose statin regimen was not modified (72.2% vs 52.8%; $p = 0.0294$).

Conclusion: The low occurrence of therapeutic modifications and goal attainment may indicate a need for greater awareness of the importance of effective statin use.

Coronary heart disease (CHD) is the leading cause of mortality in the US.[1] Currently, 12.9 million Americans have been diagnosed with CHD.[1] Elevated low-density lipoprotein-cholesterol (LDL-C) levels have been identified as a major cause of CHD, however dyslipidemia is a modifiable risk factor. Inhibitors of HMG-CoA reductase, more commonly known as statins, are the most effective agents for the reduction of LDL-C levels.[2]

Despite the abundance of literature supporting the benefits of statins for the lowering of LDL-C levels, numerous studies have found that patients are not achieving the LDL-C targets put forth by the National Cholesterol Education Program (NCEP).[3-7] Marcelino and Feingold[5] found that among patients who received statin therapy for a 1-year period, only 33% achieved their LDL-C goal. The multicenter Lipid Treatment Assessment Project (L-TAP) found that only 18% of patients with CHD who were treated in an outpatient setting achieved their target LDL-C goal. While adherence to diet, exercise, and lipid-lowering medication are important factors in attaining LDL-C goals, statin titration has also been recognized as a contributing factor.[8] Recent evidence has shown that, for many patients, statins are not being titrated and

consequently, patients are not achieving their LDL-C targets.[7-9] Therefore, the purpose of this study was to characterize statin utilization patterns and evaluate LDL-C goal attainment among patients treated with statins in a population of managed care enrollees.

The primary objective of this study was to characterize statin utilization patterns during a 1-year period after the initiation of statin therapy. These objectives were achieved through a primary analysis, which examined outcomes among patients who were initiated on statin therapy, and secondary analysis, which examined the types of modifications to statin regimens. Investigations of the utilization patterns included identification of the initial statin, adherence, and the occurrence, type, and frequency of therapeutic modification. Time to first therapeutic modification was also determined. An exploratory analysis was conducted in a sub-group of patients with available laboratory data. The primary objective of this exploratory analysis was to determine therapeutic outcomes, in terms of LDL-C level reduction and goal attainment.

Methods

Study Design and Data Source

This study was a retrospective cohort analysis of claims (pharmacy and medical), enrollment and laboratory data from Prescription Solutions®, [1] a pharmacy and medical management organization. This large managed care organization covers 3.3 million people in eight states (Arizona, California, Colorado, Nevada, Oklahoma, Oregon, Texas, and Washington). This database has been used in previous healthcare service and economic studies.[10-15]

The primary analysis was conducted to analyze the data of all patients who were prescribed a statin during the period from 1 January 2001 to 31 December 2001. A secondary analysis was conducted among all patients who had a therapeutic modification in their statin regimen. For all patients, the specific statin first prescribed was defined as the index statin. All pharmacy claims for statins and other cholesterol-lowering medications during the 1-year follow-up period were used to identify therapeutic modifications that represented an increase in the potency of the lipid-lowering regimen. Dose response (for LDL-C level reduction), based on the information provided in each statin's package insert, was used to determine statin potency. Select cutpoints (as used in a previously published study):[16] low potency ≤30% LDL-C level reduction; moderate potency 31–40% LDL-C level reduction; high potency ≥41% LDL-C level reduction.

For each patient, the dosage of each statin prescription dispensed was compared with the dosage of the previously dispensed statin prescription. Once a change was noted, the date of the pharmacy claim with the new dosage and the date of the previous dispensation were identified. If a prescription for any other cholesterol-lowering medication was filled, the first dispensation was marked as a modification event. Time to first therapeutic modification was determined by counting the number of days between the index date and the date of the therapeutic modification. The frequency of therapeutic modification was determined and reported by counting the number of therapeutic modifications per study patient. For patients who underwent more than one modification event, each modification event was treated as being independent.

An exploratory analysis was conducted among a subset of patients from the primary analysis who had laboratory values available to enable evaluation of LDL-C levels and goal attainment. Two main cohorts were identified: (i) those who received a modification in their statin regimen; and (ii) those who did not receive a modification in their statin regimen.

Patient Selection

Members were included in the analysis if they were newly initiated on any of the following statins during the identification period: atorvastatin, fluvastatin, lovastatin, pravastatin, or simvastatin. The index date was defined as the date of the first pharmacy claim for any of the aforementioned statins during the identification period. Newly treated patients were defined as those who had not been dispensed any of the aforementioned statins for the 6-month period before the index date. Patients were excluded if they (i) were <8 years of age at the index date; (ii) possessed a pharmacy claim for a statin during the 6-month period prior to the index date; or (iii) were not continuously enrolled in the health plan during the 6 months prior to or 12 months after the index period. Patients who met study criteria for the primary analysis were eligible for the secondary analysis if they had received a therapeutic modification to their statin regimen, defined as:

- an increase of any magnitude in the dosage of the index statin (e.g. atorvastatin 10mg to atorvastatin 20mg);
- a switch to a different statin or regimen with a potency that would be considered to be an increase in strength (e.g. simvastatin 40mg to atorvastatin 20mg);
- an addition of another cholesterol-lowering medication.

1 The use of trade names is for product identification purposes only and does not imply endorsement.

Table I. Coronary heart disease (CHD) risk factor categories

Low risk for CHD – evidence of one or less of the following factors
ICD-9-CM diagnosis code representing hypertension: 401.x, 402.xx, 403.xx, 404.xx, 362.11, 437.2
ICD-9-CM diagnosis code representing smoking: 305.1, V15.82
ICD-9-CM diagnosis code representing a family history of ischemic heart disease: V17.3
Age/gender: >44 years old and male or >54 years old and female
High-density lipoprotein level <40 mg/dL
Triglyceride level ≥200 mg/dL
Moderate risk for CHD – evidence of two or more of the following risk factors
ICD-9-CM diagnosis codes representing hypertension: 401.x, 402.xx, 403.xx, 404.xx, 362.11, 437.2
ICD-9-CM diagnosis codes representing smoking: 305.1, V15.82
ICD-9-CM diagnosis code representing family history of ischemic heart disease: V17.3
Age/gender: >44 years old and male or >54 years old and female
High-density lipoprotein level <40 mg/dL
Triglyceride level ≥200 mg/dL
High risk for CHD – CHD or CHD risk equivalent
Evidence of CHD
ICD-9-CM diagnosis code representing CHD: 410.xx, 411.xx, 412.xx, 413.xx, 414.xx.
ICD-9-CM procedure codes representing CHD 36.0x, 36.1x.
CPT: 33510 – 33536, 33572, 92975 – 92977, 92980 – 92984, 92995 – 92996
Evidence of diabetes mellitus
ICD-9-CM diagnosis code representing diabetes: 250.xx, 362.01, 362.02, and 366.41.
Two or more filled prescriptions for an antidiabetic (i.e. insulin or oral antihyperglycemic drugs) within any 90-day period
Evidence of other clinical forms of atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm, and symptomatic carotid artery disease)
ICD-9-CM diagnosis codes representing ASHD: 429.2, 433.xx, 434.0x, 434.9x, 435.x, 436, 437.0, 437.1, 440.xx, 441.xx, 443.xx.
ICD-9-CM procedure codes representing ASHD: 38.12, 38.13, 38.14, 38.15, 38.16, 38.18, 38.34, 38.44, 39.22, 39.23, 39.24, 39.25, 39.26, 39.28, 39.29, 39.50, 99.10.
CPT representing ASHD: 34800 – 34832, 33877, 35081 – 35103, 35301, 35390, 35311 – 35381, 35450 – 35495, 35500 – 35683

ASHD = atherosclerotic heart disease; **CPT** = Current Procedural Terminology; **ICD-9-CM** = International Classification of Diseases, Ninth Revision, Clinical Modification.

Finally, patients who met study criteria through the primary analysis were eligible for the exploratory analysis if they had at least two measured LDL-C levels and at least two pharmacy claims for a statin. The first LDL-C measurement must have been performed within the 90 days prior to the initiation of statin therapy. The second LDL-C measurement must have been performed at least 30 days after the initiation of statin therapy.

Outcome Variables: Primary Analysis

Outcomes of interest were the identity of the index statin, whether the index statin was dispensed only once during the 1-year post-index period, the medication possession ratio (MPR) and adherence and persistence with therapy. The occurrence of therapeutic modification, frequency of therapeutic modification and time to first therapeutic modification during the 1-year follow-up period were determined. Finally, predictors of therapeutic modification were identified and reported.

The statin MPR was defined as the sum of days supply for all dispensations of statins, divided by the number of days of therapy between the first and last dispensations plus the days of supply for the last dispensation. The days supplied for prescriptions that exceeded the study period were truncated to the end of the study period. When the calculation resulted in an MPR that was higher than 1.0, the MPR value was truncated to 1.0. The statin adherence rate was defined as the sum of days supply for all dispensations divided by the total days in the post-index period. Statin persistence was also determined. A patient was deemed persistent if they filled a prescription for a statin within 60 days of the end of the supply provided by the previous prescription; the number of days of persistence during the post-index period was calculated.

Table II. Baseline demographic and clinical characteristics for enrollees in a managed care organization who were newly initiated on a statin medication[a]

Total number of patients	38 567
MediCare + choice (%)	56.7
Female (%)	50.6
Age (years) [mean ± SD]	63.6 ± 13.4
Chronic Disease Score (mean ± SD)	3.1 ± 2.8
NCEP ATP III coronary heart disease risk status (%)	
low	45.1
moderate	15.7
high	39.2
Medical history	
hypertension (n [%])	14 570 (37.8)
coronary heart disease (n [%])	6837 (17.7)
congestive heart failure (n [%])	2012 (5.2)
COPD (n [%])	1977 (5.1)
cerebrovascular accident (n [%])	1140 (3.0)
transient ischemic attack (n [%])	734 (1.9)
diabetes mellitus (n [%])	7707 (20.0)
depression (n [%])	1120 (2.9)
cardiac reperfusion procedure (n [%])	1518 (3.9)
at least one hospitalization for acute illness during the pre-index period (n [%])	4890 (12.7)
Total healthcare charges incurred during the pre-index period ($US, mean [SD])	8824 (28 631)

a Statins included atorvastatin, fluvastatin, lovastatin, pravastatin, or simvastatin.

COPD = chronic obstructive pulmonary disease; **NCEP ATP IIII** = National Cholesterol Education Program Third Adult Treatment Panel guidelines.

Other variables included were the age at the index date, sex, the Chronic Disease Score (CDS), the NCEP Third Adult Treatment Panel (ATP III) guidelines risk status, and select co-morbid conditions. Von Korff and colleagues[17] developed the CDS as a measure of chronic disease status using population-based automated pharmacy claims. Risk categories (low, moderate, and high) [table I] were based on NCEP ATP III risk determinants and were modified to obtain data from retrospective claims.

The primary outcome of interest for the secondary analysis was the type of therapeutic modification. The primary outcomes of interest for the exploratory analysis were the LDL-C level reduction achieved and whether the reduction achieved resulted in patients attaining their LDL-C goals. The LDL-C goals for high-risk, moderate-risk and low-risk patients were <100 mg/dL, <130 mg/dL and <160 mg/dL, respectively.[3]

Outcomes were stratified to compare patients who received a therapeutic modification of their antihyperlipidemic regimen with those who did not. To determine patients' LDL-C goals, patients were first categorized into risk categories (table I) and then assigned an LDL-C goal.[3] Other variables reported were age at the index date, sex, CDS, and select co-morbid conditions.

Statistical Analysis

The outcome variables for all analyses were described using means, standard deviations, percentages, and counts. The primary and exploratory analyses were descriptive. When conducting the secondary analysis, a bivariate analysis was conducted to identify significant associations between select variables and the occurrence of a therapeutic modification event. A multivariate logistic regression model was then developed to determine the collective influence of these variables. All reported p-values were two-sided with an alpha level of 0.05. A Kaplan-Meier survival curve was used to describe the number of days until a therapeutic modification for the five index statins. All statistical analyses were performed using SAS® version 8.2 software (Cary, NC, USA).

Results

Primary Analysis

Demographic and Clinical Characteristics

The final study cohort consisted of 38 567 patients. Baseline demographic and clinical characteristics are displayed in table II. The most commonly prescribed statin at index was pravastatin

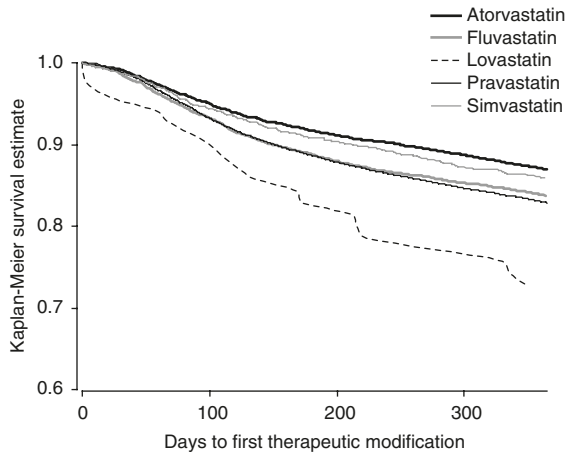

Fig. 1. Time to first therapeutic modification event: survival analysis for risk of therapeutic modification.

Table III. Results of the multivariate logistic regression model for a therapeutic modification event for enrollees in a managed care organization who were newly initiated on a statin medication[a]

Covariates	df	Class	Odds ratio (95% CI)	p-Value
Age	1	Incremental increase in age by 1 year	0.988 (0.986, 0990)	<0.0001
Sex	1	Female vs male	0.931 (0.880, 0.984)	0.0117
Index HMG-CoA reductase inhibitor potency	2	Low vs high	2.867 (2.463, 3.338)	<0.0001
		Moderate vs high	1.144 (1.002, 1.306)	<0.0001
Index HMG-CoA reductase inhibitor	4	Atorvastatin vs pravastatin	0.791 (0.724, 0.865)	0.8667
		Fluvastatin vs pravastatin	0.577 (0.523, 0.636)	<0.0001
		Lovastatin vs pravastatin	1.010 (0.588, 1.732)	0.2914
		Simvastatin vs pravastatin	0.713 (0.626, 0.811)	0.1219
Acute hospitalization during the pre-index period	1	Yes vs no	1.188 (1.080, 1.305)	0.0004
Cardiac reperfusion procedure during the pre-index period	1	Yes vs no	1.349 (1.161, 1.569)	<0.0001

a Statins included atorvastatin, fluvastatin, lovastatin, pravastatin, or simvastatin.

df = degrees of freedom.

(63.5%), followed by atorvastatin (17.9%), fluvastatin (12.5%), simvastatin (5.9%), and lovastatin (0.2%). Of the entire cohort, 16.4% (n = 6320) were dispensed only one statin prescription during the entire post-index period. The mean statin MPR and adherence rates were 0.83 ± 0.21 and 0.55 ± 0.33, respectively. The mean number of days of persistence with statin therapy was 214.7 ± 134.

Of the 38 567 patients who met study criteria, there were 7405 distinct therapeutic modifications among 6220 (16.1%) members. Of those who received a therapeutic modification, 84.4% (n = 5251) had their statin regimen modified once, 13.2% (n = 824) had their statin regimen modified twice, and 2.3% (n = 145) had their statin regimen modified three or more times.

Time to Therapeutic Modification

The median time to a therapeutic modification was 125 days. Kaplan-Meier survival estimates were calculated to display the proportion of members who have not yet received a therapeutic modification over the time in days, stratified by the five index statins (figure 1).

Predictors of a Therapeutic Modification

Logistic regression analysis was used to develop a model to predict therapeutic modification events. Multivariate analysis showed significant predictors of regimen modification included age, sex, index statin, index statin potency, and the occurrence of a cardiac reperfusion procedure or acute hospitalization during the 6-month pre-index period ($p < 0.05$). The odds ratio estimates for the logistic regression model are displayed in table III.

Secondary Analysis: Therapeutic Modification Events

Demographic and Clinical Characteristics

As previously stated, there were 7405 distinct therapeutic modifications among 6220 (16.1%) members and each therapeutic modification was treated as an independent event. The mean age of patients who experienced modification of their statin regimen was 61.8 ± 13.1 years and 52.2% were male. The mean CDS was 3.2 ± 2.9, and more patients were classified as being at low risk according to NCEP ATP III criteria (43.0%), than were categorized as being at high (41.6%) or moderate risk (15.4%).

Type of Therapeutic Modification

The most common type of therapeutic modification was an increase in the index statin dosage (72.4%), followed by a switch to another statin that resulted in an increase in potency (14.4%), the addition of another lipid-lowering medication (12.9%), an increase in dose and the addition of another lipid-lowering medication (0.25%), and a switch to another statin that resulted in an increase in potency and the addition of another lipid-lowering medication (0.08%).

Exploratory Analysis: Evaluation of Low-Density Lipoprotein Cholesterol (LDL-C) Values and Goal Attainment

Clinical Characteristics

For the exploratory analysis of the study, the cohort consisted of 254 patients (see Patient Selection section in Methods for eligibility criteria). Of these, 85.8% (n = 218) did not receive a therapeutic modification to their statin regimen while 14.2% (n = 36) had received a therapeutic modification. The mean age of the cohort was 66.6 ± 10.5 years and 57.9% of patients were female. Clinical characteristics at baseline are displayed in table IV.

LDL-C Levels: Relative Reduction and Goal Attainment

Among this subgroup, the mean baseline LDL-C level was 183.0 ± 56.8 mg/dL and patients required a mean percentage reduction of 33.0 ± 19.0% to attain their goal level. The mean LDL-C at follow-up was 123.2 ± 38.5 mg/dL, which represents a mean reduction of 25.8 ± 36.8%; 55.5% of patients attained their LDL-C goal. When stratified by therapeutic modification (yes/no), goal attainment was significantly higher among patients whose statin regimen was modified compared with patients whose stain regimen was not modified (72.2% versus 52.8%; p = 0.0294).

The patients who were categorized as being at low risk had a mean baseline LDL-C level of 178.1 mg/dL and required a mean percentage reduction of 25.4% ± 16.7% to attain their goal. The mean LDL-C at follow-up was 128.7 ± 41.9 mg/dL, which represents a mean reduction of 19.4% ± 42.9%, and 77.1% of patients attained their LDL-C goal.

In patients categorized as being at moderate risk, the mean baseline LDL-C level was 178.9 mg/dL and patients required a mean percentage reduction of 25.2% ± 16.8% to attain their goal. The mean LDL-C at follow-up was 118.2 ± 34.3 mg/dL, which represents a mean reduction of 28.9% ± 27.8%, and 76.4% of patients attained their LDL-C goal.

Patients categorized as being at high risk, had a mean baseline LDL-C level of 188.3 mg/dL and required a mean percentage reduction of 42.2% ± 17.6% to attain their goal level. The mean LDL-C at follow-up was 121.7 ± 34.3 mg/dL, which represents a mean reduction of 29.0% ± 36.4%, and 30.2% of patients attained their LDL-C goal.

Discussion

There were several notable findings in this study. Despite the abundance of research supporting the benefit of statins for lower-

Table IV. Exploratory analysis: clinical characteristics of enrollees in a managed care organization who met the criteria for subanalysis[a]

Parameter	Therapeutic modification		
	no	yes	all
No. of patients (% total patients)	218 (85.8)	36 (14.2)	254 (100.0)
Chronic Disease Score (mean [SD])	3.73 (3.11)	4.08 (3.33)	3.78 (3.14)
NCEP ATP III risk status (n [% patients in therapeutic modification strata])			
low	68 (31.2)	15 (41.7)	83 (32.7)
moderate	48 (22.0)	7 (19.4)	55 (21.7)
high	102 (46.8)	14 (38.9)	116 (45.7)
Select co-morbid diseases (n [% patients in therapeutic modification strata])			
hypertension	105 (48.2)	16 (44.4)	121 (47.6)
coronary heart disease	47 (21.6)	9 (25.0)	56 (22.0)
congestive heart failure	8 (3.7)	3 (8.3)	11 (4.3)
chronic obstructive pulmonary disease	20 (9.2)	6 (16.7)	26 (10.2)
cerebral vascular accident	11 (5.0)	2 (5.6)	13 (5.1)
transient ischemic attack	5 (2.3)	0 (0.0)	5 (2.0)
cardiovascular reperfusion procedure	0 (0.0)	1 (2.8)	1 (0.4)
diabetes mellitus	59 (27.1)	8 (22.2)	67 (26.4)
depression	10 (4.6)	2 (5.6)	12 (4.7)

a Patients were eligible if they had at least two measured low-density lipoprotein-cholesterol levels and at least two pharmacy claims for a statin.

NCEP ATP IIII = National Cholesterol Education Program Third Adult Treatment Panel guidelines.

ing LDL-C levels, of the entire cohort, 16.4% of the patients who were initiated on a statin possessed only one pharmacy claim for these medications during a 1-year period. This finding was consistent with previously published studies that reported a rate of 12–15% of patients filling only one prescription for a statin during a 1-year follow-up period.[18,19]

Of those patients whose statin regimen was modified, the median time to a therapeutic modification was 17.8 weeks. This is slightly longer than expected, as NCEP's ATP III guideline recommends evaluating the LDL-C response, and if necessary, intensification of treatment, at approximately 6–12 weeks. An interesting finding was that when medication was in the patient's possession (as evidenced by the presence of a pharmacy claim), they tended to be compliant and had a relatively high MPR.

While the size of the cohort for which laboratory data were available was limited, a few interesting findings were noted. In this study, we found that, overall, 55.5% of the patients attained their LDL-C goal according NCEP's ATP III LDL-C target goals. This is somewhat higher than that cited in medical literature.[7] In the secondary and exploratory analyses of this study only 16.1% and 14.2% of the patients, respectively, had received a therapeutic modification that resulted in an increase in the potency of their lipid-lowering regimen. If the aim of statin therapy is to achieve ATP III LDL-C goals, and therapeutic modification may be necessary to achieve this goal, it is unclear why we found therapeutic modification, particularly among those who were at high risk, to be such an uncommon event.

Finally, patients categorized as being at high risk for CHD, irrespective of whether they received a therapeutic modification, possessed the highest mean reduction in LDL-C level; however, this reduction was insufficient as only 30.2% of this group attained their LDL-C goal. Although, this group possesses the lowest LDL-C goal, this still represents a problem, as these are the patients who should have their lipid levels aggressively managed. Additionally, CHD events may incur a substantial amount of healthcare resources, as well as having a negative impact on quality of life.

As with all studies, biases or unknown confounding factors may have influenced our study findings. The use of pharmacy claims data denotes that only prescriptions that have been filled through our claims processing system are included in this analysis. It is possible that physicians had prescribed changes in patients' medication regimens that would have been considered therapeutic modifications, but that these were not filled by patients or were filled somewhere outside the coverage of the pharmacy and medical management organization. Moreover, compliance and MPR were utilized as proxy measures of medication adherence. Therefore, it cannot be assumed that because prescription claims were submitted, representing use, the patient actually consumed the medication or consumed it as prescribed. Finally, the exploratory analysis cohort was of a relatively small sample size as our eligibility criteria for this section of the analysis required LDL-C testing at select points in time in relation to statin initiation. Therefore, it is difficult to determine whether this small sample is representative of the entire population. In addition, utilizing measured LDL-C values and including only patients with private insurance and full health and drug benefits may limit the generalizability of the results. Despite these and other potential confounders, the information derived through this retrospective analysis is compelling, and consistent with available evidence suggesting that few patients with dyslipidemia are managed aggressively and attain their LDL-C targets.

Conclusion

The low occurrence of therapeutic modifications and goal attainment may indicate a need for greater awareness of the importance of using statins effectively. In addition, a multifaceted approach, which involves the patient, physician, and healthcare system, may be the most effective approach toward LDL-C goal attainment.

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