

Analysis of Factors Associated With Statin Adherence in a Hierarchical Model Considering Physician, Pharmacy, Patient, and Prescription Characteristics

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ABSTRACT

BACKGROUND: Adherence with maintenance drug therapy such as HMG-CoA reductase inhibitors (statins) is typically analyzed from the perspective of patient characteristics.

OBJECTIVE: To determine the effects of physician and pharmacy characteristics in addition to patient characteristics on variation in adherence rates for 4 statin drugs (atorvastatin, pravastatin, rosuvastatin, and simvastatin) for patients who patronized only 1 pharmacy and 1 prescriber of a statin.

METHODS: A retrospective cohort study of 6,436 patients who initiated statin therapy was performed from computerized pharmacy records of 2 large national pharmacy chains. Adherence was defined as the number of 30-day refills within 12 months after initiation of statin therapy. Physician, pharmacy, prescription, and patient covariates were considered in a cross-classified hierarchical regression model.

RESULTS: The average number of refills dispensed was 4.75 per patient. Patients younger than 50 years had, on average, 13.6% fewer refills per year than did patients older than 70 years ($P < 0.001$). Women were 4.4% less adherent than men ($P = 0.041$). Patients residing in southern states were significantly less adherent than were other patients; they had 19.4% fewer refills per year than did patients from western states ($P < 0.001$). Each prescription dispensed for comorbid conditions increased adherence by 2.0% ($P = 0.002$), and patients with a history of cardiovascular drug use were 14.1% more adherent than were other patients ($P < 0.001$). Patients on a higher statin dose appeared to be 8.4% less adherent than were patients on a lower dose ($P < 0.001$). Adherence was greater as the number of prescribed refills increased, with a rate of 2.1% per refill ($P < 0.001$). Adherence was lower for patients with higher copayments, with a rate of 2.2% per each additional \$10 of copayment ($P < 0.001$). For patients treated by physicians in the top 2.5 percentile and bottom 2.5 percentile of statin adherence, mean refill counts per year were 6.1 and 2.9, respectively. For patients who patronized pharmacies in the top 2.5 percentile and bottom 2.5 percentile of statin adherence, mean refill counts per year were 6.6 and 2.5, respectively. Adherence increased at a rate of 28.4% per each additional 100 statin patients per patronized pharmacy ($P < 0.001$) and decreased at a rate of about 6.5% per each additional 10 statin patients per treating physician ($P < 0.001$).

CONCLUSION: Because of the variability in adherence rates across pharmacies and physicians, further assessment of pharmacy and physician characteristics in addition to patient characteristics may be of value in improving adherence.

KEYWORDS: Adherence, Variation, Hierarchical model, Statins, Persistence

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What is already known about this subject

- The majority of patients for whom statins are prescribed in routine clinical practice either stop taking the drug altogether or take less than the prescribed dose.
- To date, most studies of adherence have studied only the effects of patient characteristics on patient adherence. Few studies have examined how much of a variability in patient adherence outcome is attributed to an individual physician, and no studies have been published on how much is attributed to an individual pharmacy.

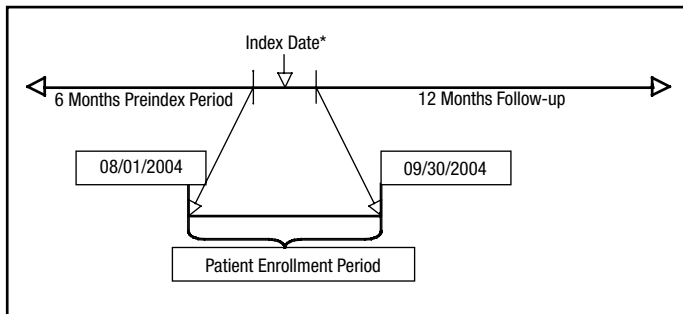
What this study adds

- To our knowledge, this study is the first attempt to assess the amount of variation in adherence that can be attributed separately to physicians and pharmacies, after adjusting for patient case mix.
- Adherence was greater as the number of statin patients using a particular pharmacy increased, at a rate of 28.4% per each additional 100 statin patients per pharmacy. A significant inverse relationship was observed between the number of statin patients treated by a given physician and adherence: adherence decreased at a rate of about 6.5% per each additional 10 statin patients per physician.
- For patients who patronized pharmacies in the top 2.5 percentile and bottom 2.5 percentile of statin adherence, mean refill counts per year were 6.6 and 2.5, respectively. For patients treated by physicians in the top 2.5 percentile and bottom 2.5 percentile of statin adherence, mean refill counts per year were 6.1 and 2.9, respectively.

There are many efficacious medications available today to treat and prevent conditions of considerable morbidity and mortality. However, in the majority of cases, treatment success is suboptimal. The most common reason for treatment failure is lack of adherence to the prescribed drug therapy. In general, fewer than 50% of patients receiving long-term treatment adequately adhere to their prescribed regimens, regardless of their disease state.¹⁻³ A low level of medication adherence for conditions such as diabetes, hypertension, hypercholesterolemia, and congestive heart failure is associated with a higher level of disease-related medical costs.⁴

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FIGURE 1 Graphical Display of the Study Design



* Index date is the date of an initial prescription for atorvastatin, rosuvastatin, pravastatin, and simvastatin (excluding simvastatin with ezetimibe) between August 1, 2004, and September 30, 2004.

For medications that prevent future morbidity, such as lipid-lowering and antihypertensive drugs, it has been particularly difficult to achieve high levels of adherence. The efficacy of lipid-lowering therapy in reducing the burden of coronary heart disease (CHD), the leading cause of death in the United States, is well established.⁵⁻⁹ HMG-CoA reductase inhibitors (statins) can significantly reduce the incidence of CHD and mortality from acute myocardial infarction. However, adherence to statin regimens is critical for the successful prevention of CHD. The majority of patients for whom statins are prescribed in routine clinical practice either stop taking the drug altogether or take less than the prescribed dose. Cohort studies of patients who were prescribed statins show variable and often high rates of therapy discontinuation.¹⁰⁻¹² Simons et al. reported that only about 50% of patients who were prescribed a lipid-lowering drug were still taking it 6 months later.¹³ The percentage of adherent patients dropped to 30% to 40% after 12 months.^{13,14}

There are many barriers to adherence, including lack of education, cost of treatment, low physician trust, side effects, inadequate provider-patient communication, and convenience factors.¹⁵⁻¹⁷ No standard strategy exists for improving adherence. Several comprehensive pharmacy care programs have been used that have improved patient adherence and outcomes. A new multiphase study published by Lee and colleagues tested medication adherence in community-based patients aged 65 years and older who received usual care compared with continued pharmacy care (standardized medication education, regular follow-up by pharmacists, and medications dispensed in a time-specific manner). This intervention improved medication adherence and persistence and resulted in meaningful clinical reductions in blood pressure; discontinuation of the program resulted in lower medication adherence and persistence.¹⁵

Other clinical studies have also shown a positive impact on patient medication adherence. Project ImPACT took place at 26 community-based ambulatory care pharmacies. As part of the triangle of care (patient, pharmacist, and physician), pharmacists actively educated patients about the risks associated with high cholesterol levels, the importance of controlling their cholesterol levels, and treatment goals. Pharmacists also conferred with physicians on the type of medication needed for each patient. This study demonstrated that clear communication and collaboration between patients, pharmacists, and physicians could result in improved adherence, enabling patients to reach their treatment goal.¹⁸

Other studies have shown that poor relationships and/or poor communication between patient and physician can lead to low rates of adherence. Piette and colleagues examined the role of patient-physician trust in medication adherence. They found that when physician trust levels were low, patients were more likely to forgo medication treatment.¹⁶ Young and colleagues assessed physician information-giving habits across internists and family physicians prescribing antidepressants. The results showed that physicians provided limited information to patients and frequently did not discuss information critical to improving adherence to therapy.¹⁹

One of the challenges for planning effective interventions to improve medication adherence is to identify the weakest element in the chain from prescribing to persistent use by patients. If such targets for intervention can be identified, then relatively expensive programs developed to improve adherence can become more cost-effective. Strategies and interventions to improve adherence on the individual patient level are highly variable and include adherence aids, refill or follow-up reminders, regimen simplification, various subsidies such as coupons and rebates, written and oral education, and comprehensive medication and disease management.²⁰ Aside from patients, physicians and pharmacies are potential intervention targets. The main objective of our analysis is to assess the relative importance of pharmacies and physicians on the variation in patient adherence to statin therapy. An additional goal is to examine the effects of patient-, prescription-, and provider-level characteristics on statin adherence.

Methods

Patients

A retrospective cohort study was performed for patients who initiated statin therapy. The data for this study were obtained from blinded computerized pharmacy prescription records of 2 national pharmacy chains representing more than 4,300 community pharmacies nationwide. Data contained prescription drug activity for all prescriptions filled at these national chains for each individual patient, regardless of health care plan. Patients were selected on the basis of the presence of an initial prescription for atorvastatin, rosuvastatin, pravastatin, or

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simvastatin between August 1, 2004, and September 30, 2004 (Figure 1). Other statins (i.e., fluvastatin, generic lovastatin, and simvastatin with ezetimibe) constituted less than 3% of all statin prescriptions and were not included in the analysis because of the low volume.

The date of the first statin dispensing during the study period was the index date of the analysis. Only patients who had no statin dispensed in the 6 months before the index date in the same pharmacy chain were included in the study (Figure 2). The analysis was restricted to include index prescriptions with only a 30-day supply to avoid misclassifying adherence by ensuring that all study patients had an equivalent starting point. (Patients with less than a 30-day supply for the index script would have, on average, more refills than would patients with a 30-day supply, making these patients erroneously look more adherent. Conversely, patients with more than a 30-day supply for the index script would have, on average, fewer refills than would patients with a 30-day supply, making these patients erroneously look less adherent.)

Patients who filled statin prescriptions written by more than 1 physician or who patronized more than 1 pharmacy within a chain were excluded from the analysis. Patient adherence was evaluated for 1 year after the index date. The analysis was further restricted to physicians and pharmacies who represented at least 4 patients eligible for our analysis during the study period to allow for more stable multilevel estimates.

All patient identifiers were deleted after linkage, and nontraceable study ID numbers were assigned. This study was approved by the Institutional Review Board of Brigham and Women's Hospital.

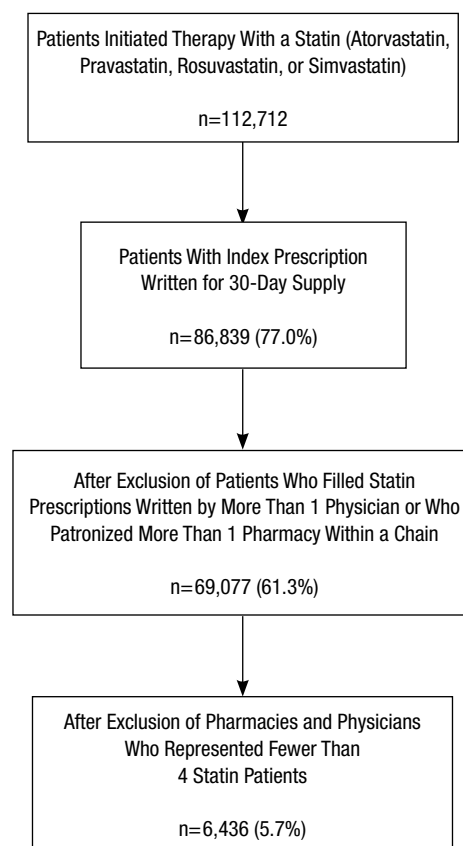
Adherence Outcome

Rates of refilling prescriptions are often used as an accurate and objective measure of overall prescription drug adherence.^{21,22} Since statin therapy is chronic in nature, we assumed that any completed prescription (i.e., new prescription plus all authorized refills) was going to be followed by a new prescription. The outcome variable was defined as the total number of 30-day refills that patients obtained during the 1-year follow-up period.

All analyses were performed at the patient level; all statin fills for each patient were summed even if they represented new prescription numbers or switches from one statin to another. Few patients (approximately 4%), however, switched to another statin during the study evaluation period.

About 4.1% of all patients selected for the analysis received the first prescription with a 30-day supply and then the following prescription(s) with a 60- or 90-day supply. For these patients, we created a proxy of 30-day refills, counting, for example, a refill with a 60- or 90-day supply as 2 or 3 refills with a 30-day supply. Patients with 11 or more refills were considered fully adherent.

FIGURE 2 Flowchart of Statin Patient Selection



Covariates

The measured patient-level characteristics included age, gender, number of existing comorbid conditions (measured using a count of Chronic Disease Score [CDS] disease categories²³), history of cardiovascular diseases (measured using the cardiovascular component of the CDS), region of residence (North-east, Midwest, South, and West), and index prescription-specific characteristics (daily dose, number of refills prescribed, and copayment). Patients' baseline comorbid conditions and history of cardiovascular diseases were identified from prescriptions filled during the 6-month period before the index date. The daily doses were grouped into high and low categories, where the low-dose category included patients with the prescribed daily doses of 10 mg or less for atorvastatin and simvastatin, 5 mg or less for rosuvastatin, and 20 mg or less for pravastatin. Physician- and pharmacy-level characteristics consisted of the total number of patients treated with lipid-lowering drugs in the enrollment period and pharmacy chain indicators.

Statistical Analysis Using Hierarchical Models

Patient, physician, and pharmacy characteristics are all important factors affecting patient-level adherence outcomes. Traditional multivariate techniques treat observations as though they were independent. However, patients in a given physician practice or pharmacy may share characteristics, and their outcomes are unlikely to be truly independent of one another. For example, a physician may tailor his/her clinical practice toward specific diseases and/or socioeconomic subgroups. At the pharmacy level, the pharmacy location, size, daily prescription volume, number of pharmacists, degree of counseling, etc., may result in less heterogeneity in the patient population. Patients associated with a physician or with a pharmacy form a natural 2-level hierarchical structure. Ignoring the clustering that exists in hierarchical data may result in a biased estimation of both parameter estimates and their variances, and therefore will result in a false statistical inference.

A statistical technique that is well suited to explore the effects of pharmacy and physician characteristics on patient adherence is multilevel modeling or random effects regression models.²⁴⁻²⁷ Additional hierarchical levels can be easily added to the model. The 2-level hierarchy of physicians and patients (1 physician sees several patients) could be expanded to include pharmacies at a third level. However, no clear hierarchy can be defined between physicians and pharmacies because patients can fill prescriptions at different pharmacies. Conversely, customers of a specific pharmacy are treated by many different physicians. In this situation, patients are said to be contained within cross-classification of physicians by pharmacies.²⁶

We will denote by $Y_i(j_1, j_2)$ the adherence outcome for patient i , treated by physician j_1 , and filling prescriptions at pharmacy j_2 , and the corresponding expected value is denoted as $\mu_{i(j_1, j_2)}$. The adherence outcome is the count of 30-day refills in 12 months. The standard distribution for counts is the Poisson distribution. However, in real-life applications, variability among counts is usually greater than would be expected by simple Poisson distribution. Such extra variability is called overdispersion. The negative binomial regression is the generalization of the Poisson regression, which takes into account the possibility of overdispersion. To account for possible overdispersion, the adherence outcome was modeled with a negative binomial distribution.^{28,29}

One of the important features of negative binomial distributions is that the variance is not a free parameter as in the case of a normal distribution, but is a function of the mean. In terms of hierarchical modeling, this leads to a relationship between the parameters in the fixed part of the model and the parameters of the random part.²⁶ To answer the question of how much variability in the patient's adherence outcome is attributable to the process occurring at the pharmacy level than at the physician level, we will consider the following cross-classified negative binomial hierarchical model:

$$\begin{aligned}
 Y_{i(j_1, j_2)} &\sim NB(\mu_{i(j_1, j_2)}), \\
 \log(\mu_{i(j_1, j_2)}) &= (X\beta)_{i(j_1, j_2)} + u_{j_1} + u_{j_2}, \\
 u_{j_1} &\sim N(0, \sigma_{u1}^2), \\
 u_{j_2} &\sim N(0, \sigma_{u2}^2),
 \end{aligned}$$

where $(X\beta)_{i(j_1, j_2)}$ is the set of linear predictors and parameters u_{j_1} and u_{j_2} represent the physician-specific and pharmacy-specific contributions to patient adherence.

Here we model the negative binomial variation at the patient level and assume that variations at physician and pharmacy levels are independent and normally distributed with means of 0 and variances of σ_{u1}^2 and σ_{u2}^2 , respectively. The log-linear nature of this regression means that the independent predictors $(X\beta)_{i(j_1, j_2)}$ and the level-2 random parameters u_{j_1} and u_{j_2} have multiplicative effects on the expected counts of refills. For example, if there is only 1 explanatory variable X_1 , the right side of the above equation is equivalent to $\exp(\beta_0) \exp(\beta_1 X_1) \exp(u_{j_1}) \exp(u_{j_2})$, where β_0 is the intercept. Therefore, each additional unit of X_1 will have the effect of multiplying the expected number of refills by $\exp(\beta_1)$.

Similarly, in a pharmacy with a high intercept, for example, 2 standard deviations, so that $u_{j_2} = 2\sigma_{u2}$, the expected number of refills will be $\exp(2\sigma_{u2})$ times as high as in a pharmacy with the average value, $u_{j_2} = 0$, of the intercept.²⁵ Another consequence of multiplicity of effects is that no simple relationship exists between the variance of an outcome and the variances of the random effects.²⁶

The significance of the fixed parameters is evaluated using 2-sided t tests. The interactions between different covariates were checked and found to be nonsignificant at the $\alpha = 0.1$ level. Accordingly, the final multivariate model included only main effects. The significance of the random parameters is evaluated by the Wald test, comparing the estimates divided by their standard errors with a standard normal distribution. Because the variance components are bounded by 0, the null hypotheses of no variance ($H_0: \sigma_{uk}^2 = 0, k=1, 2$) are tested against the 1-sided alternative hypotheses ($H_1: \sigma_{uk}^2 > 0, k=1, 2$).

Parameter estimation in the above hierarchical generalized linear model is done by restricted pseudo-likelihood methods as implemented in the SAS GLIMMIX procedure (SAS v. 9.13, Cary, NC).³⁰

Results

The final cohort consisted of 6,436 patients initiating statin therapy at 586 pharmacies prescribed by 1,059 physicians. Table 1 lists baseline patient and prescription characteristics. The average age of the patients was 59.9 years (SD=13.1, range 8-101) and 49.8% were female. The mean statin copayment for the index prescription was \$28.64 (SD=\$32.67, range \$0-\$377.50). Patients had, on average, 2.0 (SD=2.0, range 0-12) prescriptions dispensed for comorbid conditions (defined by CDS categories); more than 27% of patients had no prescrip-

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TABLE 1 Characteristics of 6,436 Patients at the Time of the Index Statin Prescription

Characteristic		Characteristic	
Age (years)		History of cardiovascular drug use†	43.9%
Mean [SD]	59.9 [13.1]	Pharmacy chain	
≤50	24.3%	A	9.0%
51-60	30.4%	B	91.0%
61-70	23.2%	No. of prescriptions dispensed for comorbid conditions	
>70	22.1%	Mean [SD]	2.0 [2.0]
Gender		0	27.5%
Female	49.8%	1	20.6%
Region of residence*		2	18.3%
Northeast	5.5%	3	13.2%
Midwest	31.8%	>3	20.4%
South	21.1%	No. of index refills prescribed§	
West	41.6%	0	21.1%
Index dose of statin drug‡		1	7.1%
High dose	67.8%	2	11.3%
Low dose	32.2%	3	16.7%
Index prescription copayment		4	3.6%
Mean [SD]	\$28.64 [\$32.67]	5	16.9%
<\$1	15.5%	6	9.0%
\$1.10-\$10	21.0%	7-10	1.8%
\$10.10-\$50	46.0%	11-12	12.5%
>\$50	17.5%		

* Northeast states: CT, MA, ME, NH, NJ, NY, PA, RI, and VT; midwest states: IA, IL, IN, KS, MI, MN, MO, ND, NE, OH, SD, and WI; southern state: AL, AR, DE, FL, GA, KY, LA, MD, MS, NC, OK, SC, TN, TX, VA, WV, and Washington DC; western states: AK, AZ, CA, CO, HI, ID, MT, NM, NV, OR, UT, WA, and WY.

† Used during 6 months prior to the index date. Drug groups 31-40, defined by Medi-Span Generic Product Indicator (GPI) therapeutic classification system.

‡ Prescriptions were grouped into high and low categories, where the low-dose category was defined as a daily dose 10 mg or less for atorvastatin and simvastatin, 5 mg or less for rosuvastatin, and 20 mg or less for pravastatin.

§ PRN (as-needed) refills were coded as 12 refills prescribed.

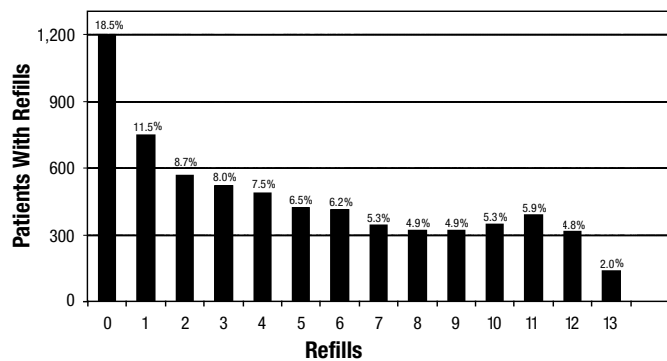
tions for other conditions. Almost half of all patients (43.9%) had a prior history of cardiovascular medication use (Table 1). The mean number of statin patients per physician was 9.8 (SD=7.0, range 4-46) and the mean number of statin patients per pharmacy was 63.3 (SD=35.4, range 10-264).

Figure 3 displays the observed frequency of refills picked up. The distribution is highly right-skewed, with 18.5% of all patients not picking up any refills. The average number of refills dispensed was 4.7 (SD = 4.0, range 0-13) per patient. The variance is considerably greater than the mean, indicating that a negative binomial distribution is an adequate assumption for distribution of refills. The large variance of the outcome signifies that a relatively big sample size is required to estimate the effects of various prognostic factors of adherence

with enough precision.

Table 2 shows results of the cross-classified multivariate hierarchical regression model of patient adherence to statin therapy. Based on the significance level, adherence was most strongly associated with the number of refills prescribed and copayment for the index prescription. Patients and index prescription characteristics that are significantly associated with adherence included age, gender, region of residence, index copayment, index dose, number of prescriptions dispensed for comorbid conditions, and prior history of cardiovascular disease. As discussed earlier, the effect of each predictor on patient adherence can be quantified by exponentiation of parameter estimates from Table 2, $\exp(\beta)$. On the basis of these calculations, we can conclude that patients younger than

FIGURE 3 Frequency Distribution of 30-Day Refills Picked Up During the 12-Month Follow-up Period*



* Patients with 11 or more refills are considered as fully adherent. Patients who consistently refilled their scripts earlier than the refill due date were able to get more than 11 refills during 12 months of follow-up.

50 years had, on average, 13.6% fewer refills per year ($\exp(\beta)=0.864$) than did patients older than 70 years ($P<0.001$). Women were 4.4% less adherent than were men ($P=0.041$). Patients residing in southern states had 19.4% fewer refills per year than did patients from western states ($P<0.001$). Each comorbid condition increased adherence by 2.0% ($P=0.002$) and patients with a history of cardiovascular drug use were 14.1% more adherent than were other patients ($P<0.001$). Patients on a higher statin dose appeared to be 8.4% less adherent than were patients on a lower statin dose ($P<0.001$). Adherence was greater as the number of prescribed refills increased, with a rate of 2.1% per refill prescribed ($P<0.001$). Adherence was lower for patients with a higher copayment, at a rate of 2.2% per each additional \$10 of copayment ($P<0.001$).

At the second level of our hierarchical structure, adherence was greater, as the number of statin patients using a particular pharmacy increased, with a rate of 28.4% per each additional 100 statin patients per pharmacy ($P<0.001$). Also, a significant inverse relationship was observed between the number of statin patients treated by a given physician and adherence: adherence decreased at a rate of about 6.5% per each additional 10 statin patients per physician ($P<0.001$).

The physician- (σ_{u1}^2) and pharmacy-level (σ_{u2}^2) variance components (and their standard errors) yield the following estimates of 0.021 (0.007) and 0.035 (0.007), respectively, indicating slightly more variability across pharmacies than across physicians with respect to patient adherence to statin therapy. The variances at both physician and pharmacy levels are highly statistically significant. As mentioned earlier, random effect

parameters have a multiplicative effect on the expected counts of refills. Particularly, each expected count of refills is multiplied by $\exp(u_{j1})$ to account for the effect of specific physician and by $\exp(u_{j2})$ to account for the effect of specific pharmacy (with these multipliers equal to 1 for average values of $u_{j1}=0$ and $u_{j2}=0$). Under the assumption of normality of random effects, we would expect that patients at 2.5% of all pharmacies had at least $e^{+1.96 \sqrt{0.035}}=1.45$ more refills than did the conditional average (defined by case mix), and that patients at 2.5% of all pharmacies had at least 1.45 ($e^{-1.96 \sqrt{0.035}}$) fewer refills than did the conditional average. Therefore, we can say that patients at the upper (best) 2.5% of all pharmacies have, on average, at least 2 (1.45×1.45) times more statin refills than do patients at the lower (worst) 2.5% of all pharmacies. Similar calculations show that patients at the upper (best) 2.5% of all physicians have, on average, at least 1.75 times more statin refills than do patients at the lower (worst) 2.5% of all physicians.

For patients who patronized pharmacies in the top 2.5 percentile and bottom 2.5 percentile of statin adherence, mean refill counts per year were 6.6 and 2.5, respectively. For patients treated by physicians in the top 2.5 percentile and bottom 2.5 percentile of statin adherence, mean refill counts per year were 6.1 and 2.9, respectively.

Discussion

The study used a cross-classified hierarchical model to analyze patient adherence to statin therapy. This model estimated the relative variation in patient adherence by physician and pharmacy (random effects) after adjusting for patient, index prescription, and health care provider characteristics (fixed effects). This model was used to avoid key weaknesses of conventional (nonhierarchical) regression models, which neglect clustering of patients within pharmacies and physicians. To our knowledge, this study is the first attempt to assess the degree of variation in adherence that can be attributed separately to physicians and pharmacies, after adjusting for patient case mix.

We found that the percentage of patients on statin therapy dropped sharply after the index fill, with approximately 18% of all statin initiators not having a second fill after the index prescription. A higher number of refills prescribed and lower copayment amount for the index prescription were associated with better adherence to statin therapy. The latter result is consistent with conclusions of recently published studies that analyzed the effects of prescription drug copayments on statin adherence.^{12,31} A higher number of comorbid conditions, particularly those treated with cardiovascular drugs, was associated with a higher rate of refills, similar to the findings of other studies.^{32,33}

Our study also found high variation in adherence to statins across pharmacies and physicians that was not explained by patient case mix. The variation in adherence was larger among pharmacies than among physicians.

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TABLE 2 Parameter Estimates of Multivariate Cross-Classified Regression Model of Patient Adherence to Statin Therapy

	Parameter Estimate (SE)	Exponentiated Coefficient (exp(B))
Intercept	1.446 (0.058)*	
Fixed Effects (B)		
Age (years)		
≤50	-0.146 (0.034)*	0.864
51-60	0.026 (0.031)	1.026
61-70	0.034 (0.032)	1.035
>70	0	
Gender		
Female	-0.045 (0.022)†	0.956
Region of residence		
Northeast	0.016 (0.198)	1.016
Midwest	-0.040 (0.035)	0.961
South	-0.215 (0.040)*	0.806
West	0	
Pharmacy chain		
A	0.083 (0.049)	1.086
B	0	
No. of prescriptions dispensed for comorbid conditions	0.020 (0.007)‡	1.020
History of cardiovascular drug use	0.132 (0.026)*	1.141
Index dose of statin drug		
High dose	-0.088 (0.023)*	0.916
Low dose	0	
No. of index refills prescribed	0.021 (0.003)*	1.021
Index prescription copayment§	-0.023 (0.004)*	0.978
Volume of statin patients per physician	-0.067 (0.020)*	0.935
Volume of statin patients per pharmacy¶	0.025 (0.005)*	1.284
Random Effects		
Physicians, σ_{u1}^2	0.021 (0.007)*	
Pharmacies, σ_{u2}^2	0.035 (0.007)*	

* P value <0.001; † P value <0.05; ‡ P value <0.01; § The parameter estimate is calculated based on a \$10 increment;

|| The parameter estimate is calculated based on a 10-patient increment; ¶ The parameter estimate is calculated based on an 100-patient increment.

We observed that patients who filled their statin prescriptions at pharmacies with a high volume of statin prescriptions showed, on average, better adherence. We could not determine whether this observation was because of well-trained pharmacists in the area of cardiovascular disease at these pharmacies, disease management programs, or other factors unmeasured by our analysis.

We also found that, on average, patients treated by physicians who prescribed more statin prescriptions had a lower adherence rate than did those treated by physicians who prescribed

fewer statin prescriptions. We did not capture the medical specialty of the physicians in this study and therefore cannot speculate on the possible influence of medical specialty. However, high prescribers may have less time per patient to engage in counseling that may influence adherence to statin therapy. Previous research has shown that general practitioners have more patients using lipid-lowering medications than do specialists,³⁴ and general practitioners initiate about 80% of prescriptions for statins.³⁵ All physicians report time pressures, and primary care physicians may have less time per patient.³⁶

We focused on pharmacy and physician factors in this study, but patient characteristics have been associated with adherence to lipid-modifying therapy. We know from previous research that patients at higher risk for coronary artery disease are more likely to adhere to their treatment than are patients who take it for primary prevention.³⁷

The factors that affect clinical outcomes in lipid-modifying therapy include educating patients, monitoring their response to therapy, and having interventions targeted at behaviors of patients and prescribers.³⁸ In addition, one of the major barriers to adherence is poor communication between the physician and the patient. According to Marinker et al., patients and physicians should form a therapeutic alliance to “optimize health gain from the best use of medicines, compatible with what the patient desires and is capable of achieving.”³⁹ This is referred to as concordance. To facilitate full concordance, special training in communication may be necessary for health care providers.⁴⁰

Another opportunity for the health care provider is to identify patients with high risk for nonadherence and to be more aggressive in efforts to monitor and communicate with their patients on an individual basis. Reminding physicians about communicating with their patients regarding the importance of adherence to therapy and providing physicians with a list of their nonadherent patients can positively affect patient adherence from the perspective of population disease management.⁴¹

Improving patient adherence may be achieved through pharmacy-based programs, where a combination of patient education and provider awareness is available.⁴² Since medications are important in the treatment of chronic conditions and because pharmacists have significant knowledge of medications, they play a critical role in disease management.^{43,44} Pharmacists are the most accessible health care providers to the patient once medication therapy is initiated.³⁸ Therefore, pharmacy care models can promote behavioral changes among patients and should be an important and integral part of the overall treatment plan.

The Asheville Project assessed the clinical, humanistic, and economic outcomes of a community-based medication therapy management (MTM) program. The study found that patients with asthma or diabetes who received ongoing education and long-term MTM achieved and maintained improvements in their condition and had significantly lower disease-related costs.^{43,44}

Assessing adherence by pharmacy characteristics may be of value when it comes to improving adherence with prescribed therapy, particularly for health plans with a commitment to health maintenance. Hierarchical models, such as those employed in this study, can be used to assess unusual performance of specific physicians or pharmacies that represent patients with particularly poor adherence. These providers can be targeted by customized interventions to improve adherence. Of course, in actual practice, statistical analysis can provide only a preliminary indication of suboptimal performance, and more

detailed investigation is necessary to verify targets of opportunity for clinical practice improvement.

Limitations

This study relied on the dispensing records of 2 pharmacy chains. While this method in some ways permits more detailed examination of individual patients within a pharmacy chain, it also means that, in our analysis, a patient is lost to follow-up when he or she obtains a refill or new prescription at a pharmacy in a different chain. So the first limitation is that patients who switched pharmacy chains were considered discontinued in our analysis.

Second, exclusion of the only generic statin (lovastatin) creates a limitation of this study, particularly with respect to the relationship between copayment amount and adherence. Our study design, which required a 6-month preindex wash-out period without statin use, resulted in low counts of new generic lovastatin users. Since generic lovastatin has significantly lower cost than the brand statins, exclusion of this drug could potentially have some additional effect on the established relationship between adherence and copayment. However, more than 36% of all patients in our sample paid less than a \$10 copayment for the index script. This number is big enough to reliably assess the influence of low copayments on patient adherence.

Third, our analysis included only statin patients with index prescriptions for a 30-day supply, which resulted in the loss of about 23% of the initial patient population. This selection was made to make interpretation of the results more consistent; however, it limits the degree to which our results can be generalized to all statin patients.

Fourth, while pharmacy data are very accurate in recording actual dispensing and prescription pick-up by patients, these data lack information on whether a particular patient actually consumes the medication. However, studies have shown that dispensing data are a good marker for actual use.²¹ Assuming some nonuse of dispensed drugs, we realize that the reported adherence rates in the present study overestimate actual adherence.

Fifth, although the 2 selected pharmacy chains are nationwide and reasonably representative of the population of pharmacies, patient and pharmacy characteristics within these chains may not be representative.

Sixth, even though this analysis is adjusted for patient and health care provider characteristics, it is likely that not all characteristics that are relevant predictors of adherence were captured. For example, unmeasured patient factors such as severity of disease, patient race, English proficiency, patient income, and educational attainment may be clustered in pharmacies or physician practices and therefore may cause some residual confounding in our analysis. At the health care provider level, we didn't have information on physician gender, age, years in practice, degree, medical specialty and board training, physi-

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cian/pharmacist attitudes on the importance of counseling, the number of staff in physician offices and in pharmacies, and whether some pharmacies operated medication adherence programs.

Seventh, the present model assumes that patients are associated with a single physician or pharmacy, which may not accurately reflect real-life situations. Instead, patients can be treated by several physicians, or they can fill prescriptions at several pharmacies. Such further complexity can be taken into account by the use of so-called multiple membership models,²⁶ which are very often computationally intractable. However, statin patients using more than 1 physician or pharmacy constituted less than 16% of our original statin patient population (Figure 2), which, along with the large patient sample size and a large number of health care providers in this analysis, should make our results sufficiently robust.

Conclusions

Lack of adherence with prescribed therapy is a well-documented problem that can greatly affect patients' health outcomes. Although the current literature recognizes this problem as multifaceted, it mostly covers the role of the patients and their behavior in adhering to therapy. Our study not only examined the impact of patient characteristics on medication adherence but also examined the possible influence of the pharmacy and the physician in this critical aspect of the treatment.

Our hierarchical modeling approach revealed that there are large variations in patient adherence to statin therapy among both pharmacies and physicians, which translates into a large difference in the refill rates between the best- and worst-performing health care providers at the extreme ends of the distributions. It also showed that high-volume physician practices that prescribed more statins were associated with lower patient adherence. In contrast, pharmacies that dispensed more statins were associated with greater patient adherence to statin therapy.

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