Physician Follow-up and Provider Continuity Are Associated With Long-term Medication Adherence

A Study of the Dynamics of Statin Use

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Background: Many patients who initiate statin (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor) therapy discontinue treatment within 1 year. We sought to estimate the rate at which patients reinitiate treatment after long periods of nonadherence and to determine whether reinitiation of treatment is linked to potentially modifiable factors such as physician visits, cholesterol testing, or other encounters with the health care system.

Methods: We studied new users of statins in British Columbia, Canada, who initiated treatment between January 1, 1997, and June 30, 2004, and who had an extended period of nonadherence, defined as at least 90 days after the completion of 1 prescription in which no refill for any statin medication was obtained. Survival analysis was used to estimate the rate of reinitiation of statin therapy. Case-crossover analysis was used to evaluate the predictors of reinitiation.

Results: We identified 239 911 new users of statins, of whom 129 167 (53.8%) had a period of nonadherence that lasted for at least 90 days. Of these patients, an estimated 48% restarted treatment within 1 year and 60% restarted treatment within 2 years. Case-crossover analysis revealed events that were associated with a return to adherence, including visits with the physician who initiated the statin regimen (odds ratio [OR], 6.1; 95% confidence interval [CI], 5.9-6.3), a visit with another physician (OR, 2.9; 95% CI, 2.8-3.0), and a cholesterol test (OR, 1.5; 95% CI, 1.4-1.5). Incident myocardial infarction (OR, 12.2; 95% CI, 8.9-16.9) and other cardiovascular disease–related hospitalizations (OR, 3.6; 95% CI, 3.1-4.3) were also strong predictors of reinitiation of treatment.

Conclusions: Physicians should be aware that statin use is dynamic and that many patients have long periods of nonadherence. A follow-up visit with the physician who wrote the initial statin prescription and having a cholesterol test predicted reinitiation of statin therapy. Our results suggest that continuity of care combined with increased follow-up and cholesterol testing could promote long-term adherence by shortening or eliminating long gaps in statin use. This hypothesis should be confirmed in a randomized experiment.

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In patients with clinically evident coronary artery disease, statin (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor) therapy substantially reduces the risk of myocardial infarction (MI), stroke, and all-cause mortality.[1-4] However, despite the safety and effectiveness of statins for secondary prevention, an important body of research has found that patient adherence to long-term statin therapy is poor, with many patients becoming nonadherent by 1 year.[5-10]

Given the public health and clinical consequences of widespread underuse of statins and other effective long-term medications, there has been increasing interest in the development of strategies to improve patient adherence to prescribed therapies.[11,12] Improving adherence has been challenging, however, and only multifaceted, patient-centered interventions have been consistently found effective.[13,14] A greater understanding of the determinants of adherence to statin therapy is necessary to develop simple and cost-effective interventions.

Most previous studies of medication use have been designed to reveal correlates of poor adherence and identify groups of people at risk of discontinuing treatment.[5-9,15-19] While these studies have led to important characterizations of the problem of nonadherence to statin therapy, their designs do not readily permit the identification of modifiable determinants of adherence. To better understand patterns of statin use and factors that could be modified to improve adherence, we propose a new approach to studying medica-

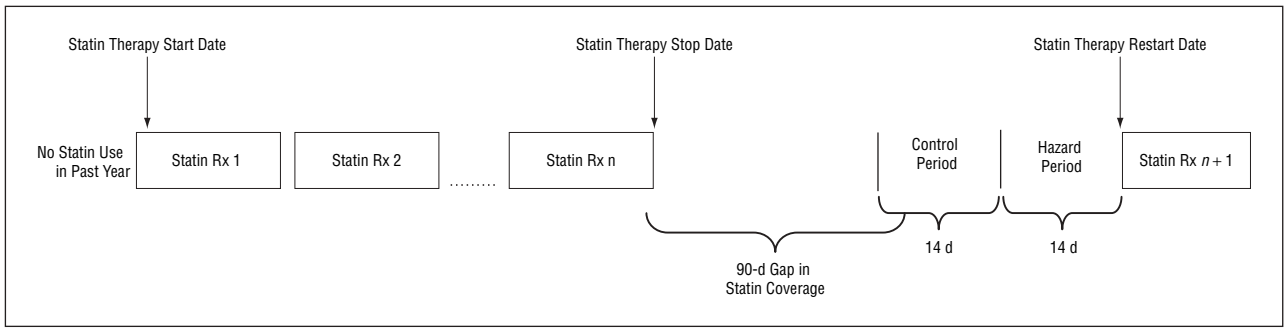

Figure 1. Schematic of case-crossover design. Rx indicates prescription.

tion use that uses a case-crossover method to identify time-varying predictors of medication refills. The case-crossover method is based on within-person comparisons and, therefore, is not confounded by subject characteristics that are constant in time.[20-22] Such studies can get closer to the causal process than cross-sectional analytic approaches. We applied this method in a study of adherence to statins in a large, new-user cohort in British Columbia, Canada. Using the case-crossover design, we explored how cholesterol testing, physician visits, and various types of hospitalizations are related to refilling a statin prescription by patients after an extended period of nonadherence.

METHODS

DATA

We studied subjects who initiated statin therapy between January 1, 1997, and June 30, 2004. Initiation was defined as filling a statin prescription without having filled one in the past 12 months. All patients were identified in the linked health care utilization databases of the publicly funded health care system of British Columbia. Regardless of payer, pharmacists enter medication name, dosage, and quantity for all dispensed prescription drugs into a single database via a provincewide network.[23] All medications for all residents, regardless of age or payer, are listed in this database. In addition, the Ministry of Health maintains linkable data for all physician services and hospitalizations. Up to 16 diagnoses for hospital discharges and 1 diagnosis for each medical service are recorded.[24] Patients were followed up until they died, disenrolled from the provincial health plan (emigrated from British Columbia), or reached the administrative end of follow-up, which was June 30, 2004.

To identify statin therapy discontinuation dates, we created a drug coverage data file for each patient. Consecutive statin prescriptions were linked together using dispensing dates and the "days supply" field. When a prescription was filled before the previous prescription should have been finished, use of the new prescription was assumed to begin the day after the end of the previous prescription. Discontinuation was defined as failing to fill a new prescription for a statin within 90 days of finishing a previous prescription. This definition was extended to 180 days in a sensitivity analysis.

The study investigators have Data Use Agreements with the Ministry of Health of British Columbia. The Partners Healthcare Institutional Review Board approved this research. All personally identifiable data were removed from the files before analysis to protect patient confidentiality.

STATISTICAL ANALYSIS

We used the Kaplan-Meier method to estimate the distribution of the time until a patient refilled a statin prescription.[25] We then performed a case-crossover analysis to determine whether particular events occurring during follow-up triggered reinitiation of statin therapy. The case-crossover approach stratifies the analysis across individuals; thus, each patient serves as his or her own control (**Figure 1**), removing the confounding effects of patient-level variables that are constant in time. The events considered were the occurrence of a visit with the physician who initiated the statin prescription, a visit with any other physician, a cholesterol test, a hospitalization because of MI, a non–MI-related cardiovascular hospitalization, or any noncardiovascular hospitalization. An MI hospitalization was identified based on the presence of an *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9*) diagnosis code of 410.xx. A non–MI-related cardiovascular hospitalization did not contain an *ICD-9* diagnosis code of 410.xx but did carry one of the following *ICD-9* codes: 401.xx-403.xx (hypertension), 411.xx-413.xx (ischemic heart disease), 415.xx (pulmonary embolism), 426.xx-427.xx (conductive defects and arrhythmias), 428.xx (congestive heart failure), 390.xx-394.xx or 398.xx (valvular heart disease), 440.xx-441.xx (arteriosclerosis and aneurysms), or 429.xx, 459.xx, or 479.xx (other diseases of heart and circulatory system).

The case-crossover analysis was implemented by comparing the frequency of events in the 14 days immediately before reinitiating statin therapy (hazard period; Figure 1) with the frequency of events in the 14 days immediately before the hazard period (control period; Figure 1). We also conducted a secondary analysis in which the hazard and control periods were lengthened to 30 days; that is, the hazard period was the 30 days immediately before reinitiation of statin therapy and the control period was the 30 days immediately before the hazard period.

To explore whether discontinuation was caused by adverse events, in the 90 days before statin therapy discontinuation, we assessed the frequency of hospitalization or outpatient visits because of rhabdomyolysis and muscle weakness (*ICD-9* codes 728.81, 728.9, 729.1, 728.87, and 728.88) or hepatic dysfunction (*ICD-9* codes 570, 573.3). All statistical analyses were performed with SAS software (version 9.1; SAS Institute Inc, Cary, NC).

RESULTS

We identified a study cohort of 253 951 patients who initiated statin therapy from 1997 through 2004. We excluded 14 017 subjects who initiated cerivastatin therapy,

Table 1. Baseline Characteristics of Subjects in Sample*

Characteristic	Value
No. of subjects	129 167
Male sex	72 461 (56.1)
Age, mean ± SD, y	59.6 ± 12.2
Comorbid conditions, mean ± SD	0.8 ± 1.2
Different medications, mean ± SD	2.6 ± 2.7
Physician visits, mean ± SD	14.3 ± 12.7
Acute care hospitalizations	21 188 (16.4)
Emergency department visits	16 041 (12.4)
Myocardial infarction	8822 (6.8)
Hypertension	35 906 (27.8)
Diabetes mellitus	12 125 (9.4)
Congestive heart failure	4632 (3.6)
Angina	22 694 (17.6)
Previous CABG or PTCA	8026 (6.2)
Peripheral vascular disease	3503 (2.7)
Ischemic stroke	3363 (2.6)
Initial medications	
Atorvastatin	64 883 (50.2)
Fluvastatin	6638 (5.1)
Lovstatin	8585 (6.7)
Pravastatin	18 842 (14.6)
Rosuvastatin	1349 (1.0)
Simvastatin	28 870 (22.4)

Abbreviations: CABG, coronary artery bypass grafting; PTCA, percutaneous transluminal coronary angioplasty.
*Data are given as number (percentage).

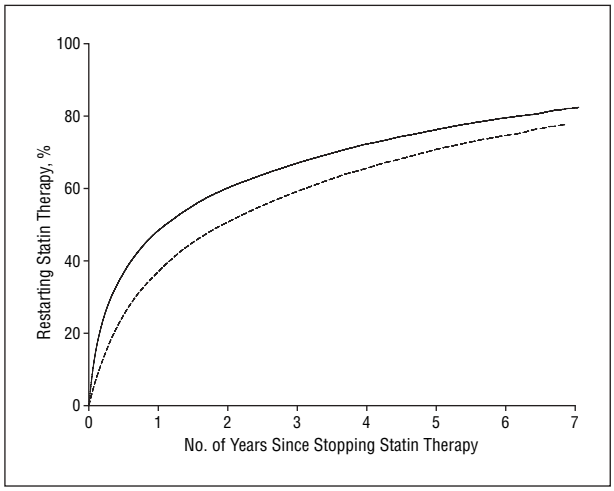

Figure 2. Kaplan-Meier estimate of the cumulative probability of returning to treatment. Solid line indicates the probability of restarting statin therapy in a cohort in which stopping therapy is defined as a period of at least 90 days after the completion of 1 prescription in which no refill for any statin medication was obtained. In this cohort, the index date is 90 days after the completion of the last prescription; dotted line, the probability of restarting statin therapy in a cohort in which the definition of stopping is extended to a period of at least 180 days after the completion of the last prescription.

which was withdrawn from the market in 2001, and 23 subjects who had prescriptions for multiple statins on the same day, leaving a population of 239 911. Of these new users, 129 167 (53.8%) had a period of nonadherence that lasted for at least 90 days. The characteristics of this sample are given in **Table 1**. These patients had a mean±SD age of 59.6±12.2 years, were predominantly men, and had a mean±SD of 0.8±1.2 comorbid condition. In the year before initiation of statin therapy, approximately 12.4% had an emergency department visit, 6.8% had a history of MI, and 16.4% had an acute care hospitalization. Among these patients, 73 291 (56.7%) ultimately restarted treatment, 3196 (2.5%) were censored by death, 3393 (2.6%) were censored by disenrollment from the provincial health plan, and 49 287 (38.1%) reached the end of follow-up without returning to regular use. **Figure 2** shows Kaplan-Meier estimates of the survival function for time to restart therapy. An estimated 48% of 129 167 patients restarted treatment within 1 year, and 60% within 2 years.

Table 2 gives the frequency of events in both the hazard and control periods. All events studied were more frequent in the 14 days before restarting statin therapy than in the 2 weeks before that. Almost half the patients who restarted statin therapy had a visit with the index physician in the 2 weeks before refilling the prescription. Almost 80% of patients had a visit with some physician during that time.

Table 3 gives the results of the case-crossover analysis. The event most strongly associated with a return to adherence was an incident MI (odds ratio [OR], 12.2; 95% confidence interval [CI], 8.9-16.9). Visits with the physician who initiated the statin regimen (OR, 6.1; 95% CI, 5.9-6.3), a visit with another physician (OR, 2.9; 95% CI, 2.8-3.0), a cholesterol test (OR, 1.5; 95% CI, 1.4-1.5), and other cardiovascular disease–related hospitalization (OR, 3.6; 95% CI, 3.1-4.3) were also strongly associated with a return to adherence. Noncardiovascular hospitalizations (OR, 1.7; 95% CI, 1.5-1.9) were moderately associated with restarting statin therapy. In a secondary analysis, we assessed whether the analysis was sensitive to increasing the duration of the hazard and control periods to 30 days. The results were qualitatively similar (Table 3, column 2); however, all effects were slightly attenuated with the exception of cholesterol testing, which increased in strength (OR, 2.4; 95% CI, 2.4-2.5). Increasing the definition of discontinuation to 180 days without any available statin therapy slightly increased the effect of a visit with the index physician (OR, 6.5; 95% CI, 6.2-6.8) and the effect of other cardiovascular disease-related hospitalization (OR, 4.3; 95% CI, 3.5-5.4) but had little effect on other parameter estimates. This change decreased the number of people who were estimated to return to treatment to 51% by 2 years from 60% (Figure 2). To assess whether treatment interruptions were owing to medication switching, we made a cross-tabulation of drugs used before and after an observed interruption in treatment (**Table 4**). Although there was a trend toward switching to atorvastatin, 65% of patients returned to using the same statin. Of those patients who returned to using the same statin, 80% continued using the same dose, 15% used a higher dose, and 5% used a lower dose.

Adverse events may have accounted for a few of the observed treatment discontinuations. A total of 87 patients (0.07%) had a diagnosis of hepatic toxicity in the 90 days before discontinuing statin therapy and 256 (0.2%) had a diagnosis of rhabdomyolysis or muscle weakness. Both events were negatively associated with restarting statin therapy after discontinuation ($P<.05$).

Table 2. Frequency of Events in Control Period* and Hazard Period† From Case-Crossover Analysis‡

Event	14-Day Control Period	14-Day Hazard Period	30-Day Control Period	30-Day Hazard Period
Physician visits				
Index physician§	12 818 (17.5)	34 603 (47.2)	18 734 (25.6)	39 548 (54.0)
Other physician	18 269 (24.9)	30 060 (41.0)	26 396 (36.0)	37 775 (51.5)
Any physician	28 127 (38.4)	57 494 (78.5)	38 307 (52.3)	63 853 (87.1)
Cholesterol testing	6689 (9.1)	15 180 (20.7)	6570 (9.0)	22 518 (30.7)
Hospitalizations				
Myocardial infarction	71 (0.1)	645 (0.9)	82 (0.1)	696 (1.)
Other cardiovascular disease	244 (0.3)	870 (1.2)	346 (0.5)	1100 (1.5)
Noncardiovascular	691 (0.9)	1195 (1.6)	1307 (1.8)	1909 (2.6)

*Period 14 to 7 days before refill.
†Period 0 to 6 days before refill.
‡Data are given as number (percentage).
§Wrote a patient's first statin prescription.

Table 3. Results from Case-Crossover Analysis: Events Predicting Return to Adherence*

Event	14-Day Hazard and Control Periods	30-Day Hazard and Control Periods
Physician visits		
Index physician†	6.1 (5.9-6.3)	5.0 (4.8-5.2)
Other physician	2.9 (2.8-3.0)	2.4 (2.4-2.5)
Cholesterol testing	1.5 (1.4-1.5)	2.4 (2.4-2.5)
Hospitalizations		
Myocardial infarction	12.2 (8.9-16.9)	8.0 (6.2-10.3)
Other cardiovascular disease	3.6 (3.1-4.3)	3.0 (2.6-3.5)
Noncardiovascular	1.7 (1.5-1.9)	1.3 (1.2-1.4)

*Data are given as multivariate adjusted odds ratio (95% confidence interval).
†Wrote a patient's first statin prescription.

COMMENT

In a population of new users of statins, we found that most patients had at least 1 extended period of nonadherence during the study period. Of patients who became nonadherent, most returned to regular use, revealing that statin adherence is dynamic, similar to other health-related behaviors.[26,27] Many previous studies have reported that patient adherence with statin regimens is poor, but, to our knowledge, this is one of the few articles indicating that many patients refill prescriptions for statins after long periods of nonuse. Given this observation, it is natural to wonder what can be done to help patients avoid interruptions in their statin regimen.

We found that the process of restarting statin therapy is strongly linked with a physician visit, particularly a visit with the (index) physician who initiated the statin regimen. This suggests that both increased physician follow-up and continuity of care could improve adherence to statin therapy by shortening or eliminating the frequent gaps in treatment. Although we expected that physician visits would lead to reinitiation of therapy in some patients, the magnitude of this effect is impressive. Indeed, most of the observed restarting of treatment occurs immediately after a physician visit. The particularly strong association between a visit with the physician who initiated the statin regimen and reinitiation of therapy is also surprising, with almost half of patients restarting treatment less than 2 weeks after a visit with that physician. The physician who initiated the statin regimen should be aware of the patient's statin prescription and is likely to inquire about adherence and stress the need for reinitiation of statin therapy if the patient has discontinued treatment. Cholesterol testing combined with a physician visit seems to have a synergistic effect, further increasing the likelihood of reinitiation of statin therapy. It is possible that the results of the cholesterol test or just the process of testing reminds a patient of his or her disease risk and the need for treatment.[28] It is also possible that physicians who order cholesterol tests are more likely to discuss with the patient the importance of continued statin therapy.[29]

Our finding that physician visits and cholesterol testing are associated with reinitiation of statin therapy is in agreement with previous research that found that patients who had a cholesterol test or a physician visit during the 3 months after initiating a statin regimen were more likely to remain adherent during the subsequent follow-up,[30] as well as studies of other medications in which it was found that the scheduling of a follow-up appointment was associated with better medication adherence.[31,32] The present study strengthens the validity of these important findings through the use of a case-crossover design that uses each patient as his or her own control and, thus, eliminates confounding caused by unmeasured patient characteristics that do not change in time (eg, general health-seeking tendencies). In the contrasting population-level study designs, it cannot be determined whether physician visits cause improved adherence or whether patients who are more likely to visit their physician, ask for cholesterol tests, and schedule follow-up appointments are more likely to remain adherent. The case-crossover design mitigates the potential for such confounding. By focusing only on patients who return to refill a prescription after a prolonged period of nonadherence, the case-crossover approach addresses the question, Why do these patients return to refill a prescription now?

Table 4. Cross-Tabulation of Statin Used Before and After Interruption in Adherence

Statin Initiated*	No. of Subjects	Type of Statin Reinitiated†						
		Atorvastatin	Cerivastatin	Fluvastatin	Lovastatin	Pravastatin	Simvastatin	Rosuvastatin
Atorvastatin	33 279	81.5	2.9	0.7	0.5	2.8	8.4	3.1
Fluvastatin	4519	38.3	6.7	35.4	1.2	6.2	11.0	1.1
Lovastatin	6131	35.1	4.2	1.4	43.3	5.3	9.6	1.0
Pravastatin	12 474	33.6	4.6	1.1	1.0	49.3	9.0	1.5
Simvastatin	16 741	27.1	3.8	0.9	0.9	3.6	61.5	2.2

*Because of small cell sizes, patients starting rosuvastatin therapy are excluded.
†Percentage of the number of subjects.

Despite its strengths, the case-crossover design may be confounded by unmeasured time-varying patient characteristics, such as a patient's perception of disease risk or the benefit of statin therapy. One explanation for our results is that information obtained during a visit with a physician changes a patient's opinion of the importance of statin therapy, leading the patient to reinitiate treatment. Another plausible explanation is that something outside of the health care system alters a patient's perception of the importance of statin therapy and that precipitates a physician visit, cholesterol test, and subsequent reinitiation of statin therapy. Because a patient's perceptions of the risks of disease and the benefits of treatment with statins are unmeasured and time-varying characteristics, the case-crossover study cannot remove confounding by these factors and, therefore, cannot help us select between these 2 competing explanations of our results.

We believe that it is more likely that patients are reinitiating statin therapy at the direction of their physician. The case-crossover analysis focused on patients who had not used a statin for at least 3 months. If these patients became concerned about their cardiovascular risk, they could return to the pharmacy for a refill or, if they needed to renew their prescription, request a refill by telephone. Regardless of the causal mechanism, the findings of our study reveal that it is relatively uncommon for patients to reinitiate treatment without a physician visit. Efforts to increase the frequency of physician follow-up can only increase the likelihood of restarting medications and, thus, should improve adherence outcomes by shortening or eliminating long gaps in statin use.

We found that hospitalizations because of MI and other cardiovascular diseases were strong predictors of a new prescription refill, although these events were uncommon and preceded few reinitiations of treatment. The occurrence of these events certainly reminds a patient of his or her disease risk and presents a compelling reason to reinitiate treatment. This finding suggests that education about the real risks associated with statin nonadherence might be effective in promoting adherence. The occurrence of a hospitalization also puts the patient in contact with physicians who have the opportunity to reassess and adjust the patient's medication regimen.

Our findings must be interpreted in light of several important limitations. First, our study may have limited generalizability. We studied a heterogeneous population in British Columbia that includes patients with a wide variety of prescription drug coverage plans, from total coverage of all prescription drugs to coinsurance with a high deductible. The results could be different in a US population that may have different economic and social barriers to adherence.

Second, our study is based on administrative data. Recorded hospital discharge and outpatient diagnoses are not perfect measures of clinical conditions, and it is possible that there could be some misclassification of test or procedure codes. However, measurement error of these exposures of interest would be not be differential (ie, they would be equally likely in the hazard and control periods) and, therefore, should only attenuate effect estimates. Similarly, the pharmacy data capture what medications were filled at the pharmacy, but we do not know how a patient is using the medication. Patients who seem to have stopped refilling their statin prescription may still be taking the medication continuously but infrequently. Nevertheless, the strong association between events such as a physician visit and a prescription refill strongly suggests that adherence behavior can change abruptly. For some patients, however, the behavior change may be from underuse to regular use rather than from nonuse to use.

Third, we are unable to assess the reasons why patients start or stop taking a medication. Thus, some of the gaps in treatment that we observed could be physician-directed. For example, the interruption could represent a pause in therapy because of an adverse event or concern about one. Given the relative safety of statins and the low recorded incidence of diagnoses of hepatic toxicity, rhabdomyolysis, and muscle weakness in patients in the study, this is not a likely explanation for many of the treatment gaps we observed.

Physicians should be aware that long periods of nonadherence are common among users of statins. Our study shows, however, that patients often restart statin therapy after long periods of nonuse. The process of patients reinitiating treatment seems to be strongly related to factors that are, in part, under the control of individual physicians. While the exact mechanism remains unclear, our results suggest that physicians have an integral role in promoting long-term patient adherence through continuity of patient care, frequent follow-up, and regular cholesterol testing. Additional experimental research focused on determining the optimal frequency of follow-up and cholesterol testing could lead to improvements in evidence-based guidelines for the treatment of patients with elevated cholesterol levels.

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