

Effect of Dispensing Supply on Pravastatin Refill Adherence

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Coronary heart disease (CHD), including acute events such as myocardial infarction and angina pectoris, is responsible for more than half of all cardiovascular deaths in the United States and also is a major cause of disability.¹ In 2002, total costs associated with cardiovascular disease were estimated at \$329.2 billion, with two-thirds being healthcare related.² Management of multiple risk factors, including reduction in low-density lipoprotein cholesterol (LDL-C), decreases CHD morbidity and mortality.

As outlined in treatment guidelines, the National Cholesterol Education Program strongly supports the use of HMG-CoA reductase inhibitors, also known as statins, to reach LDL-C target goals for both secondary and high-risk primary prevention populations.³ In terms of duration of treatment, statins are considered chronic maintenance medications that are pharmacologically effective when taken as directed.^{4,5} Poor adherence, along with step-down and discontinuation, limits statin effectiveness and is associated with return to pre-medication cholesterol levels and loss of cardioprotection.⁶⁻⁹

Although adherence to pravastatin has been estimated to be as high as 82% to 85%, statin adherence patterns appear to be similar in all respects to other chronic medication-taking behavior, for which rates range from 40% to 76%.^{10,11} Reduced adherence and discontinuation of newly prescribed statin therapy may be attributed to (1) patient misperceptions about need for treatment, (2) poor efficacy, and (3) adverse events.^{12,13} A PubMed search (January 1990-2008) with the search terms *adherence, medications, cardiovascular, measure, and dispensing supply* in the title failed to identify any current or recent studies investigating dispensing supply as a factor associated with adherence.

Various drug benefit strategies aim to control prescription drug spending while balancing the effect on health outcomes. In this study, the rationale behind a new benefit design initiative for a 30-day supply was to curb drug costs by minimizing wastage of selected formulary chronic

ABSTRACT

Objective: To examine changes in refill adherence after implementation of a mandatory 30-day refill program instead of a 90-day refill program in noninsured adults taking pravastatin for treatment of hyperlipidemia.

Study Design: Retrospective pre-post analysis of refill records (n = 708 patients) from a computerized paid claims database for a 14-month period (July 2001 through September 2002) was done in this observational cohort study of unlinked, cross-sectional assessments.

Methods: Eligible subjects were enrolled in a healthcare program providing prescription benefits to noninsured San Francisco residents. Exclusion criteria were refills of pravastatin paid either out-of-pocket or through a nonparticipating prescription benefit plan, history of fewer than 2 fills, and receipt of a quantity other than a 90-day or 30-day supply of pravastatin. A continuous, single-interval measure of medication availability (CSA) was calculated by obtaining an adherence value for each pravastatin dispensation.

Results: After adjustment for pharmacy site, age, pravastatin strength, supply, number of fills, and time trend by using robust regression, a significant difference in adherence was observed for the 2 dispensing supplies. Dispensing supply was directly correlated to CSA ($P < .001$). With CSA of 1.0 representing 100% adherence, the median observed pravastatin CSA for a 90-day supply was 0.96, and for a 30-day supply it was 0.68.

Conclusion: Optimum pravastatin refill adherence was observed with a 90-day dispensing supply in noninsured adults, including indigent and low-income adults. This result suggests a desirable benefit plan option for long-term, chronic therapy in this population.

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medications (eg, pravastatin) by the patient because of “lost medications,” earlier-than-anticipated discontinuation, changes in dosing, and stockpiling. There was a concern, however, that barriers such as increased transportation costs would override motivation to receive essentially free medication. The counterbalancing viewpoint was that the large number of participating pharmacies allowed for improved access and would neutralize any hypothetically imposed burden. The purpose of this study was to examine pravastatin refill adherence after implementation of a mandatory 30-day refill program in place of a previously offered 90-day refill program in an uninsured population.

METHODS

Study Design

Retrospective pre- versus post-policy analysis of refill records from a computerized paid pharmacy claims database was done in this observational cohort study of unlinked, cross-sectional assessments. Claims originated from a large healthcare organization in Northern California, the Community Health Network San Francisco (CHNSF), that provides healthcare and a prescription benefit program primarily to noninsured, indigent, or low-income residents of San Francisco County. Patients are eligible to participate in the program if they provide acceptable identification, declaration, and verification to an eligibility worker of the following: San Francisco residence, prior gross monthly income of under 500% of the federal poverty level, possession of financial resources within Medicaid guidelines for real and personal property, liquid assets less than 100% of the federal poverty level for outpatient and emergency services, and cooperation with pursuing other sources of reimbursement that could reasonably be expected to pay for the services provided. Cooperation includes provision of all required information on other coverage, pursuing third-party liability, and application for any programs for which the patient is potentially eligible. Enrollees may fill prescriptions without a required prescription copayment at the county hospital pharmacy or at other local retail community pharmacies that accept CHNSF coverage.

Study Population

Eligible subjects included all adult participants in CHNSF who had picked up a pravastatin prescription at eligible pharmacies at any time during the 14-month study period of July 1, 2001, through September 1, 2002. Continuous coverage by CHNSF was assumed because insurance status data could not be confirmed throughout

PRACTICAL IMPLICATIONS

Poor adherence to lipid-lowering therapy can accelerate coronary heart disease, a major cause of cardiovascular deaths and disability.

- Policymakers are challenged with development of a rational prescription benefit program that controls prescription drug costs while balancing the effect on health outcomes in the growing noninsured population.
- This study describes the effect of dispensing supply on pravastatin refill adherence in noninsured, indigent, and low-income patients with hyperlipidemia.
- Superior pravastatin refill adherence was observed with a 90-day dispensing supply versus a 30-day supply and suggests a desirable benefit plan option for chronic therapy. Improved understanding of utilization preferences provides leverage in benefit design.

the study period and because qualification for alternative prescription benefit programs would immediately nullify eligibility for CHNSF. Information on sex, race, housing status, mode of transportation, and health literacy was not available through enrollment. Exclusion criteria were refills of pravastatin paid either out-of-pocket or through a nonparticipating prescription benefit plan during the study period, history of fewer than 2 fills during the study period, same-day refills, and receipt of a quantity other than a 90- or 30-day supply of pravastatin. These criteria were selected to ensure repeated fills for each patient during the study period in order to compute an adherence score.

Data Collection

Pharmacy claims data were generated by interfacing the healthcare organization's electronic medical record and prescription paid claims with the Pharmaceutical Care Network (PCN; now SXC Health Solutions), a pharmacy benefit manager. The 14-month study period comprised the 7 months before and the 7 months after the mandated 30-day refill program was implemented on February 1, 2002. A washout window of 30 days on both sides of the index date was used to filter data. Data provided by PCN included pharmacy site, medical record number, age, pravastatin drug strength, quantity dispensed, days supply provided, and dispensing date. Site, either county hospital outpatient pharmacy or contracted community retail pharmacy (eg, Walgreens, Rite Aid), and supply (30- or 90-day) were recoded as dichotomous variables, and all time components were converted to continuous variables. Time of first and last fills, absolute duration on pravastatin, and rate

of fill were computed. The total number of pravastatin fills also was recorded. To conform to the Health Insurance Portability and Accountability Act, all personal identifiers were removed before data analysis.

Outcome Measure

Adherence was defined as the extent to which a patient followed a prescribed treatment plan, with prescription refill activity acting as a surrogate marker of medication-taking behavior.¹⁴⁻¹⁷ This definition permits estimation of the highest possible level of medication possession with acceptable reliability and exhibits error rates comparable to those of other assessment methods.^{16,18} Associations with clinical outcomes also have been reported.¹⁸ Continuous, single-interval measure of medication availability (CSA) is a measure preferred for calculating adherence in studies with high participant dropout rates. We anticipated this scenario as likely reflecting the volatility of insurance coverage that fluctuates with employment status and Medicaid eligibility. With CSA, each refill episode is calculated independently, and participants who fill only 1 prescription do not have the same weight in a cumulative analysis as participants who have multiple refills. As a result, it provides a more accurate picture of adherence distribution and allows exploratory modeling in a nonnormal distribution. In a recent systematic literature review, CSA was comparable to other measures of calculating adherence from administrative data.¹⁸

The CSA was calculated by obtaining an adherence value for each pravastatin dispensation.¹⁸ The days supply of pravastatin (30 or 90 days) was divided by the number of days in the interval from the dispensation date up to, but not including, the next dispensation date (or through the study completion date). This calculation provided an adherence value for each participant between dispensations. The mean of all dispensation adherence values provided an overall study adherence value. Analysis was performed in terms of inverse CSA to make errors more normally distributed. Values of 1.0 represented on-time refills, values of <1.0 represented late refills, and values of >1.0 represented early refills. Prior to conducting analyses, all variables were screened for outliers and missing data. Each ratio obtained was rounded to the nearest hundredth.

The CSA equals the days supply obtained at the beginning of an interval divided by the number of days in the interval. For example, a patient receiving a 90-day supply of medication who picked up the next refill 110 days later would have a CSA of $90/110 = 0.82$.

Statistical Analysis

Descriptive statistics were used to characterize the study population and pravastatin adherence patterns. Summaries of frequency, mean, SD, median, quartiles, and ranges for distributions of all variables (pharmacy site, age, pravastatin strength, supply, and number of fills) were obtained. Because there was no control cohort for comparison with the intervention cohort to determine the effect of the change in days supply, a χ^2 test was performed for independence of the distribution of number of subjects with only 1 fill versus those with more than 1 fill. Bivariate relationships between independent variables and CSA, using averaged individual variables, were sequentially tested for significance ($P < .25$ was used as a preliminary cutoff for consideration in regression models). Ordinary least squares regression analysis was initially used to determine whether the results were sensitive to adjustment for potential confounders and effect modifiers. The unit of observation for the regression analysis was the individual prescription pickup. Several regression methods were used to explore the robustness of the estimates, including robust regression, rank regression, the Kruskal-Wallis test, and analysis of variance to identify relationships among the variables.¹⁹⁻²² In these models, indicator variables for each individual were included for site and days supply period (90 vs 30 days). Interaction terms were included when they were determined to be significant at an alpha level of .05 for regression analysis. Independent variables for both models included dispensing supply (90 or 30 days), dispensing site (county hospital outpatient pharmacy or contracted community retail pharmacy), age, and a linear time trend as a proxy for duration since diagnosis.

Time series plots of the outcome variable (CSA), both untransformed and transformed natural logarithms of CSA, as a function of time were plotted to identify any gross variations between the pre- and postimplementation phases.²³ This step was taken to address the potential confounder that adherence rate is inversely correlated to duration and to adjust for variability. Given data that occur in repeated, regular, temporal intervals, this method also is useful for modeling past behavior and forecasting future behavior.²³ The date at first fill during the study period, the time elapsed from the change in policy, and the date at last fill were tested for censoring of data. Statistical analyses were conducted using Stata version 9.0 (StataCorp LP, College Station, TX). All materials and study procedures were approved by the Committee on Human Research at the University of California San Francisco.

RESULTS

Study Population and Claims Data

A total of 1323 pravastatin users were identified, of whom 708 met the study's inclusion criteria. Pharmacy claims data were generated for 2676 prescription fills for the 2 dispensing supply cohorts: 90 days (217 fills) and 30 days (2459 fills) for these study participants. Forty-three (6%) of the study participants picked up medications during both the 90- and 30-day supply periods. The χ^2 test for independence of the distribution of number of patients with only 1 fill versus more than 1 fill found no difference in proportion by site or days supply ($P < .05$). Just over three-fourths (76.4%) of these fills occurred at contracted community retail pharmacy sites. The median age for patients in the 90-day supply cohort was 58.7 years (range, 38.5-85.1), and the median age for the 30-day supply cohort was 59.9 years (range, 23.6-83.5). Of the 3 available pravastatin strengths (10, 20, and 40 mg), the most commonly filled strength was 20 mg (69.4%), followed by 40 mg (20.4%). For the 90-day supply cohort, 80.2% of fills were for the 20-mg strength; for the 30-day supply cohort, 61.9% of fills were for the 20-mg strength. The median number of fills during the 14-month study period was 2.0 for the 90-day supply cohort and 3.0 for the 30-day supply cohort (Table 1). No significant difference was observed between the 90- and 30-day supply cohorts in where the prescriptions were filled: county hospital outpatient pharmacy or contracted community retail pharmacy ($P < .001$ by the Mann-Whitney test).

Medication Adherence

A significant difference between the median pravastatin CSA for the 90- and 30-day supply groups was observed (0.96 vs 0.68; $P < .001$ by the Mann-Whitney test). This result indicated that patients who received a 90-day supply of pravastatin were more timely with refills than patients who received a 30-day supply. There was no significant difference between the median CSA for medications acquired via community retail pharmacy sites (0.97) and that for medications acquired via the county hospital pharmacy (0.93).

A rank regression produced the best fit. The regression results showed that after adjustment for explanatory variables, the change in supply from

Table 1. Characteristics of Study Sample

Characteristic	Dispensing Supply	
	90 Days (n = 97)	30 Days (n = 611)
Median age, y	58.7	59.9
Dispensing site		
County hospital outpatient pharmacy	51 (19.5%)	66 (22.8%)
Community retail pharmacy	46 (4.4%)	545 (26.2%)
Pravastatin dose, mg		
10	19 (8.8%)	415 (16.9%)
20	174 (80.2%)	1522 (61.9%)
40	24 (11.1%)	522 (21.2%)
Median number of fills	2.0	3.0

90 to 30 days increased early pickup and CSA (coefficient = -234.5 , SE = 56.1). The CSA also improved slightly over the time (coefficient = -0.16 , SE = 0.02) (Table 2). Note that because of the inverse transformation, a negative coefficient implied an increase in CSA. These results were insensitive to alternative regression methods and other analyses. Several subjects appeared at both sites and during both the 90- and 30-day supply periods; deletion of these cases made no material difference in the results. No statistically significant interaction terms were found; accounting for the effect of clustered errors due to multiple pickups by the same individual had no significant effect on the estimates. Re-estimation of the rank regression with average values, using the individual as the unit of observation rather than the pickup, produced no significant changes in the results.

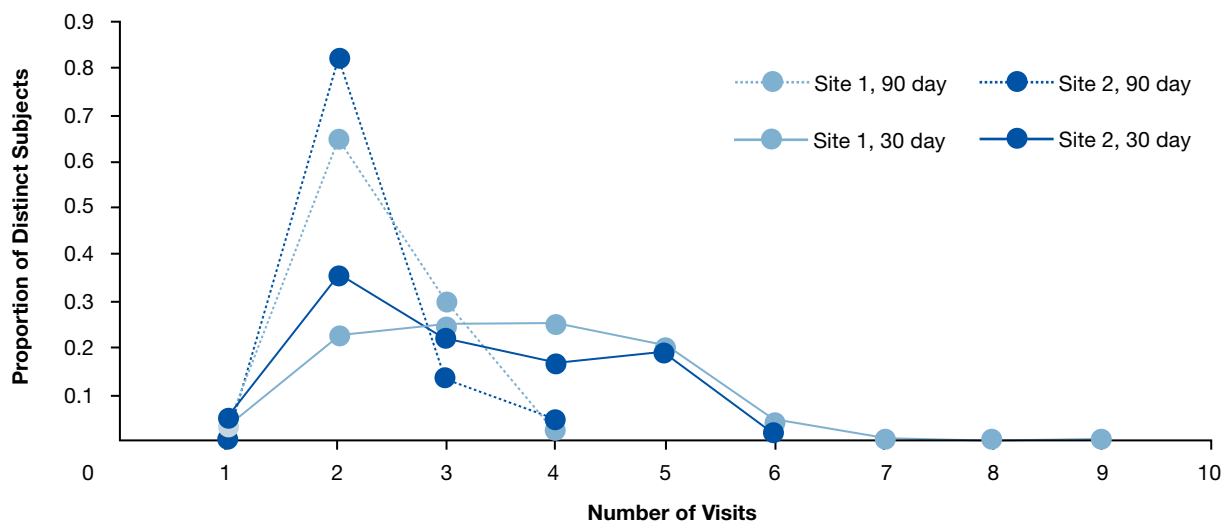
The plot (Figure 1) of the proportion of distinct patients versus the number of visits depicts utilization due to change in days supply. The plot of the natural logarithm

Table 2. Rank Regression Model Results^a

Variable	Estimated Parameters		
	Coefficient	SE	P
Constant	723.9	42.2	.000
Dispensing supply	-234.5	56.1	.000
Dispensing site	68.5	29.8	.022
Age	-0.03	0.02	.065
Time	-0.16	0.02	.000

^aDependent variable is inverse of the continuous, single-interval measure of medication availability (CSA). Dispensing supply is 0 = 90 days, 1 = 30 days. Dispensing site is 1 = hospital outpatient pharmacy, 0 = community retail pharmacy. Age is in years at time of pickup. Time is linear time trend. Overall regression is significant: $F(4, 1569) = 4.17$, $P = .0023$, $R^2 = 0.03$, $n = 1574$.

Figure 1. Distribution of Pravastatin Fills by Site and Days Supply



of inverse CSA versus dispensing date for the 90- and 30-day supply cohorts demonstrates the window of filtered data concurrent with February 1, 2002, the date of policy implementation (Figure 2).

DISCUSSION

Several issues need to be addressed before generalizing our findings to other settings. Although we did not have data regarding the original fill dates for pravastatin initiation in our patient populations, we were able to construct an accurate model that identified and adjusted for variations regardless of history of duration. Expected cumulative probability versus observed cumulative probability plots were strongly correlated in our rank regression model.

In order to make the pattern of refill behavior clear, we plotted the natural logarithm of the inverse CSA versus dispensing date. Time series analysis revealed a potentially artifactual rapid linear dropoff in adherence unique to the 30-day cohort around the 1 month washout window on each side of the policy change (Figure 2). This observation suggests censoring of data, although retrieval of paid claims data from a central computerized database should have reduced the risk of any interfacing delays and “loss” of patients who had not yet been reported from the pharmacy benefit manager.

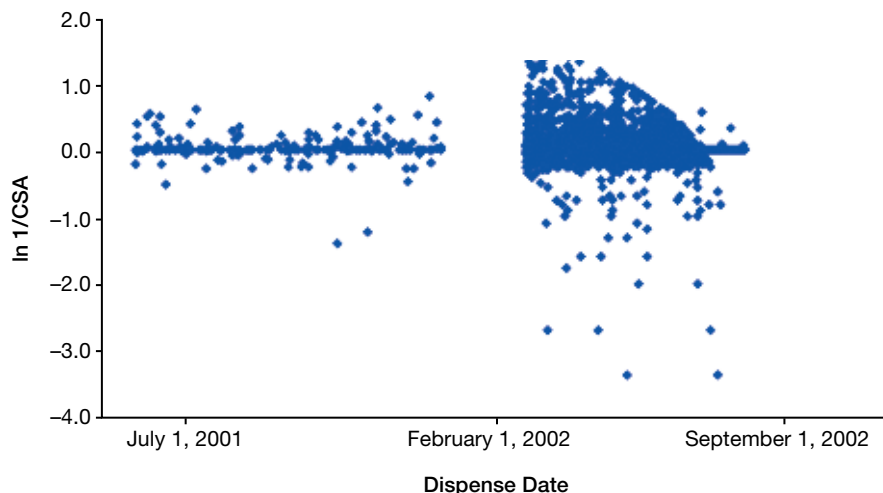
The population covered by CHNSF had high turnover, and the sample size for the 90-day supply cohort was much smaller than that for the 30-day supply cohort. This discrepancy could have been avoided by retrieving refill records further back to capture more participants with 90-

day fills. In addition, with only a small number of repeat subjects who filled pravastatin during both the 90- and 30-day observation periods, we were unable to perform longitudinal analysis of follow-up. Consequently, analysis was confined to the aggregate behavior between the 2 observation periods and the distribution of repeated fills within each observation period.

After adjustment for change in days supply and differences in the length of the sample periods, aggregate measures of utilization—number of distinct subjects and number of fills—showed a large increase during the second observation period (30-day supply). No other factors such as change in enrollment or benefit design were known to occur concurrently. This suggests that there was no evidence of a decline in utilization due to the days supply but provides little information on the policy’s effect on utilization.

The observation periods and washout were insufficiently extended to infer subject retention using the distribution of number of fills by the subject. To determine whether the dropout rate increased because of the change in days supply, we checked to see whether the proportion of patients with only 1 refill changed between supply regimens. If the 30-day supply discouraged refill, we would expect a higher proportion of subjects with only 1 fill during the 30-day supply regimen versus the 90-day regimen. The null of no change in proportion of subjects with only 1 refill could not be rejected at even the 10% level, leading us to believe that there is no evidence that the change in dispensing supply encouraged subjects to voluntarily discontinue CHNSF coverage. Although our study population

Figure 2. Plot of the Natural Logarithm of the Inverse CSA Versus the Dispense Date for the 90- and 30-Day-Supply Cohorts



CSA indicates continuous, single-interval measure of medication availability; ln= natural logarithm

was uninsured, our findings are potentially generalizable to other settings with more affluent patients who might, from a convenience standpoint, prefer a 90-day supply.

Although it is possible that an initial “micro learning curve” with the greatest decrease in adherence occurring shortly after the policy change would stabilize with time, patients may have dropped out for other reasons such as discontinuation of medication per the physician or switching to another antilipid agent after 1 to 2 months if a desired therapeutic response consistent with institution-specific formulary guidelines was not observed. That would reasonably explain the more gradual “disappearance” of many of our 90-day-supply patients and the likely dramatized effect in the 30-day-supply cohort after just a few months. Data restrictions prevented assessment of these potential confounders and the ability to distinguish barriers to adherence versus voluntary nonadherence.²⁴ Concomitant use of an adjunctive method for assessing adherence might have strengthened validity of the findings.^{25,26}

CONCLUSION

We found that dispensing supply and absolute time on pravastatin remained statistically significant in predicting CSA after adjusting for potential confounders in an uninsured population. Pravastatin refill adherence was maximized with a 90-day dispensing supply. Dispensing site was not a significant variable, indicating that pharmacy access did not appear to be an issue. These results support

studies in other populations, indicating that a 90-day supply is a desirable option.²⁷⁻²⁹ Future research with extensive data about demographics, socio-economic background, comorbidities, expenditures related to wastage of medications, tiered copayments, and follow-up of clinical outcomes over the long term will allow improved understanding of utilization preferences and evaluation of cost-effective care.

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