The Effect of Switching on Persistence and Compliance: A Comparison of Five Statins

Patrick Thiebaud, Ph.D.[1], Bimal V. Patel Pharm.D., M.S.[2], Michael B. Nichol, Ph.D.[1], David M. Berenbeim, M.D., F.A.C.P., M.B.A.[2]

[1]University of Southern California, [2]MedImpact Healthcare Systems, Inc.

BACKGROUND

In the past decade, statins have been shown to reduce the number of vascular events when used in primary and secondary prevention of CHD.[1] Statins also contribute to a lower incidence of stroke.[2] Despite the weight of evidence supporting appropriate levels of treatment, non-adherence and sub-optimal adherence remain common problems among patients treated with statins.[3] Poor compliance not only deprives patients of the benefits of treatment but can also lead to serious adverse events.[4] A better knowledge of statin utilization patterns in clinical practice and particularly the effect of switching statins—a common strategy used to help patients reach their treatment goals—is needed to improve lipid management.

OBJECTIVE

- To estimate how switching statins affects compliance and persistence
- To determine how the initial choice of statin affects compliance and persistence in the year following treatment initiation, explicitly taking into account differences between switchers and non-switchers
- To assess differences in utilization among five currently prescribed statins—atorvastatin, fluvastatin, lovastatin, pravastatin, and simvastatin

METHODS

Study Design/Data Source

- Retrospective cohort study
- MedImpact Healthcare Systems claims database

Study Cohort

- Patients are 18 and older.
- All patients are new statin users as defined by a one-year wash-out period before filling the first prescription for statin.
- Patients have been continuously eligible for benefits for two years between April 2001 and June 2004, specifically for one year before the first statin prescription and for one year after the first prescription.
- The beginning date for continuous eligibility varies from patient to patient. The date of first fill defines the index date for analysis.
- Patients who received prescriptions covering more than 30 days of supply were dropped from the sample to avoid unequal distribution of three-month supply prescriptions among drugs. Patients who filled only one prescription for a statin were also excluded to increase the chance that the remaining patients were actual users.

Table 1 Demographic characteristics, health status, and average copays.

	Atorvastatin	Fluvastatin	Lovastatin	Pravastatin	Simvastatin
N=24,035	14,416	1,401	2,254	1,880	4,084
Proportion of users	60.0%	5.8%	9.4%	7.8%	17.0%
Age (in years)*	55.1	57.8	64.6	57.7	57.5
Gender (% female)†	50.8	55.3	53.3	51.7	46.6
Comorbidities‡ (% of all patients)					
Anxiety†	15.1	15.4	18.2	16.7	14.3
Asthma	8.6	8.4	7.3	7.8	9.3
Depression†	14.6	14.8	12.5	12.3	14.0
Diabetes	11.1	11.4	11.8	10.7	11.2
Gastric Acid Disorder	13.0	11.9	12.4	11.0	12.2
Heart Disease§,||	43.7	49.0	53.0	47.3	45.8
Thyroid Disease†	7.6	9.6	9.1	9.2	7.2
Average copay‡‡,||	16.41	19.47	10.4	29.05	23.69
Difference in average copay before and after switch					-$4.29

*Bonferroni adjustment for all means, by initial drug: p<0.0001.† Chi-square, proportions, by initial drug: p<0.001.‡ Conditions with more than 5% of patients affected.§ Other than hypercholesterolemia.|| Chi-square, proportions, by initial drug: p<0.0001.‡‡ Average calculated over all prescriptions for non-switchers and all prescription filled before switching for switchers.

OUTCOMES MEASURES AND COVARIATES

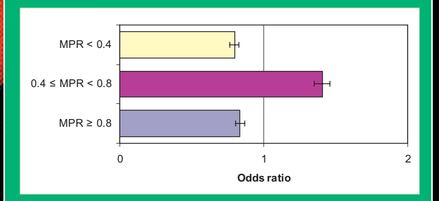
- **Compliance:** measured with the medication possession ratio (MPR), the sum of days of supply for one year after the first prescription divided by 360. Prescriptions filled later than 360 days after index date are exluded as are days of supply that occur after the end of follow-up. The MPR is calculated by assigning all statin refills or new prescriptions to the initial statin.
- **Persistence:** measured by the time to discontinuation, defined as the length of time, in days, before the first gap in medication possession. A gap is the number of days between the time patients run out of supply on their current prescription and the time they fill a new prescription. Before reaching this threshold, patients are assumed to be fully compliant. The supply of overlapping statin prescriptions is added to the total days of continuous supply. Results are shown for gap lengths of 15, 30, and 60 days.
- **Switching indicators:** it is a binary indicator for switching to another statin during the one-year follow-up and a binary indicator for dose increase from the strength of the initial statin.
- Covariates include age, gender, region, and health status as determined by RxRisk, a risk assessment system which classifies patients by their medication use in the year before their statin index date, formulary type, health plan size, average copay, year in which the treatment was started and number of drugs, besides statins, used around the index date.

STATISTICAL ANALYSIS

To control for potential selection bias due to non-random treatment assignment, the propensity score (PS) method is used to adjust for pre-treatment differences between treatment groups.[5] The PS is a patient's estimated probability of receiving the actual treatment, as calculated by a multinomial logit of all pre-treatment variables (age, gender, health status, average copay, etc.) on all treatment choices (atorvastatin, fluvastatin, lovastatin, pravastatin, and simvastatin). The inverse of the propensity score is then used to weigh each observation in the multivariate analyses. The same method was used to calculate the PS related to the probability of switching: in this case, the initial statins were added to the list of other pre-treatment predictors of switching in a logistic regression.

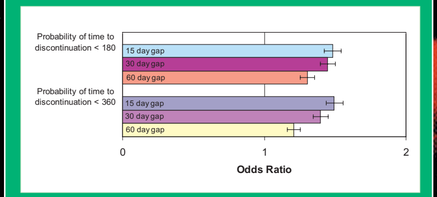
A PS-weighted logistic regression is used to determine the probability of switching from the initial statin to another in the 12 months following the index date. It is also used to evaluate the effect of treatment on the probability of being highly compliant (i.e. having an MPR $\geq$ 0.8), partially compliant (0.4 $\leq$ MPR $<$ 0.8), or being non-compliant (MPR $<$ 0.4). Another PS-weighted logistic regression is used to estimate the probability of time to discontinuation, i.e. time to first gap in treatment, greater or equal to 180 and 360 days.

Figure 1 Effect of switching on compliance



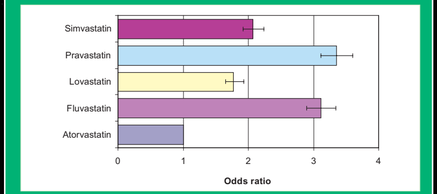
Adjusted with propensity score weights, switching reduces the odds of high compliance (MPR $\geq$ 0.8) by almost 25 percent (odds ratio: 0.768) and also reduces the odds of non-compliance (MPR $<$ 0.4). This may be due to the lack of interest in switching to a new medication among non-compliant patients.

Figure 2 Effect of switching on persistence



The effect of switching on persistence, measured as probability that time to discontinuation, or to gap, is less than 180 days or 360 days. Adjusted with propensity score weights. Probabilities above are relative to non-switchers. Switching increases the probability patients will discontinue or experience a gap in treatment before 180 and 360 days.

Figure 3 Probability of switching, by initial drug



Adjusted with propensity score weights, there are significant differences in the probability of switching, with odds ranging from 1.8 to 3.4 compared to atorvastatin. The logistic regression used here controls for differences in health status and copays as well as other predictors.

Table 2 Average medication possession ratio (MPR), proportion of patients with time to discontinuation, or to gap, less than 180 and 360 days, proportion with switch, by initial drug. Results not adjusted with propensity score weights.

	Atorvastatin	Fluvastatin	Lovastatin	Pravastatin	Simvastatin
	n=14,416	n=1,401	n=2,254	n=1,880	n=4,084
MPR*	0.69	0.66	0.65	0.65	0.67
% with time to	54.7	57.9	64.6	61.6	59.7
Discontinuation < 360 days†,‡					
% with time to	35.3	38.9	40.5	40.5	39.2
Discontinuation < 180 days†,‡					
% Switched from intitial‡	6.8	18.8	8.2	20.5	12.9

*Bonferroni adjustment for all means, by initial drug: p<0.0001.† The gap considered here has 30 days or more in length.‡ Chi-square test, all proportions, by initial drugs: <0.0001.

Table 3 Compliance measured with medication possession ratio (MPR) and persistence measured as probability that time to discontinuation, or to gap, is less than 180 days or 360 days. Adjusted with propensity score weights, by initial drug. Patients who did not switch statins.

	MPR ≥ 0.8 Odds ratio [95% C.I.]	Probability of time to discontinuation < 360. Odds ratio [95% C.I.]*	Probability of time to discontinuation < 180. *Odds ratio [95% C.I.]*
Simvastatin	0.988 (0.952, 1.026)	1.088 [1.045, 1.133]	1.067 [1.024, 1.111]
Pravastatin	0.865 [0.832, 0.898]	1.120 [1.075, 1.167]	1.129 [1.083, 1.178]
Lovastatin	0.772 (0.744, 0.801]	1.257 [1.209, 1.308]	1.246 [1.198, 1.295]
Fluvastatin	0.977 [0.942, 1.017]	1.011 [0.970, 1.054]	1.050 [1.007, 1.095]
Atorvastatin	Reference Category		

*Time to discontinuation is shown here only for gaps of 30 days or more. Results for gaps of 15 and 60 days are similar.

Lovastatin and pravastatin users are less likely to be compliant than atorvastatin users, whereas fluvastatin and simvastatin users have the same probability of compliance. Atorvastatin users are less likely to discontinue treatment than other statin users, leading fluvastatin and simvastatin users by a small margin and lovastatin and pravastatin by a more significant margin.

DISCUSSION

- Switching statins is associated with a lower probability of subsequent compliance: Patients are less likely to stay on treatment long enough to obtain maximum therapeutic benefit. The drop in compliance is all the more striking when considering that patients who switched drugs reduced their out-of-pocket costs—the average copay decreases by $4.3 after switching—a change that usually improves compliance. Other factors also play a significant role as there remain substantial differences in switching rates among statins.
- Even though the choice of initial statin affects switch rates, its influence on the compliance and persistence of patients who did not switch is much weaker. As compliance rates among non-switchers are very similar, most of the observed differences in average days covered should be attributed to differences in switch rates and the detrimental effects of switching on compliance.

REFERENCES

1. Scandinavian Simvastatin Survival Study (4S) Group. Randomized trial of cholesterol lowering in 4444 patients with coronary heart disease. *Lancet.* 1994; 344:1383-1389.

2. Morbidity and mortality: 2004 Chart book on cardiovascular, lung, and blood diseases. National Institute of Health. National Heart, Lung, and Blood Institute. 2004.

3. Ellis JJ, Erickson SR, Stevenson JG, Bernstein SJ, Stiles RA, Fendrick AM. Suboptimal statin adherence and discontinuation in primary and secondary prevention populations. Should we target patients with the most to gain? *J Gen Intern Med.* 2004; 19:638-645.

4. McDermott MM, Schmitt B, Wallner E. Impact of medication non-adherence on coronary heart disease outcomes: a critical review. Arch *Intern Med.* 1997; 157:1921-1929.

5. Imbens GW. The role of the propensity score in estimating dose response functions. *Biometrika.* 2000; 87(3):706-710.

USC UNIVERSITY OF SOUTHERN CALIFORNIA

MedImpact HEALTHCARE SYSTEMS, INC.

Presented at the ISPOR 10th Annual International Meeting Washington, DC - May 16-18, 2005