Adherence With Statins Over 8 Years in a Usual Care Setting

Shlomo Vinker, MD; Michal Shani, MD; Tuvia Baevsky, MD; and Asher Elhayany, MD

Objective: To describe adherence with statin treatment in a usual practice setting and to investigate potential determinants of better adherence.

Study Design: Retrospective cohort study using administrative claims data.

Methods: Study patients were 47,680 individuals enrolled in the Central District of Clalit Health Services HMO in Israel who filled at least 1 prescription for statins between January 1, 1999, and December 31, 2006. Data were retrieved on patients' sex, year of birth and immigration, socioeconomic status, and whether they had diabetes mellitus, hypertension, and other cardiovascular diseases.

Results: Mean age at the beginning of treatment was 61.3 ± 11.8 years; 53.3% of the study patients were women. The proportion with at least 1 chronic disease before starting statins was 40.1%; and 38.9%, 21.8%, and 9.6% of the patients were continuously adherent after 1, 3, and 6 years, respectively. Risk of discontinuation was highest among new immigrants (hazard ratio [HR] = 1.20; 95% confidence interval [CI] = 1.14, 1.27). Adherence was higher in patients having a chronic disease before starting statins (HR = 0.88; 95% CI = 0.84, 0.94) or after starting statins (HR = 0.90; 95% CI = 0.86, 0.95). Patients age <50 or >79 years had lower adherence rates. Low socioeconomic state did not affect adherence.

Conclusions: Adherence with statin therapy was poor, though adherence rates were better in patients with accompanying chronic diseases. Of particular concern was the low level of adherence in new immigrants. Intervention programs are needed and should target all patient groups.

(Am J Manag Care. 2008;14(6):388-392)

For author information and disclosures, see end of text.

Coronary heart disease (CHD) is the leading cause of death in the Western world.[1] Dyslipidemia is one of the major treatable risk factors for CHD. The introduction of statins more than a decade ago gave us for the first time an effective, convenient, and safe pharmacologic treatment to reduce serum cholesterol levels and thus prevent coronary vascular events.[2] During the last decade, the indications for treatment had been constantly expanded, and target low-density lipoprotein cholesterol (LDL-C) levels have been successively lowered.[3]

Adherence to therapy should be high in selected populations like patients with multiple risk factors, CHD, or diabetes mellitus, as the actual benefit of treatment in terms of the number needed to treat is higher.[4] Evidence suggests that in various patient populations there is a large and consistent difference between target and achieved levels of hypercholesterolemia management in both high-risk and low-risk subjects.[5-9] Statins are the cornerstone of antilipemic drug therapy and have a better adherence rate than other lipid-modifying drugs.[10] Statin therapy is becoming more common, but discontinuation and inadequate adherence continue to contribute to treatment shortfall.[6,11-13]

Recent studies have tried to focus on adherence rates and reasons for nonadherence.[10,14-16] There are different definitions for adherence[17] that may explain some of the differences between adherence rates in various studies.[5-9,14-16] But probably factors such as differences in case mixes, cultures, copayments, family physicians, and organizational structures also play a role.[15] It is important to determine the impact of background chronic diseases and sociodemographic characteristics on medication adherence. We sought to describe adherence with statin treatment over 8 years in an observational study in a usual care setting and to investigate potential predictors of better adherence.

METHODS

The study was conducted in the Central District of Clalit Health Services HMO (the largest HMO in Israel, with more than 50% of Israel's population being members). All HMO members over 25 years of age in the central district on January 1, 1998, who were still members and alive on December 31, 2006, and filled at least 1 prescription of statins were included. The overall annual rate of leaving our health plan is less than 1%.[18] Patients who dropped out of our health plan during follow-up were not included in the study cohort.

All community pharmacies in use by the HMO are computerized and report to a central repository. All prescriptions of all brands of statins, which were filled by the study population through HMO-related pharmacies, were documented. This HMO dispenses medications with nominal and almost equal copayments (between $3 and $8 for a monthly dosage), which ensures that all prescriptions were documented.

Determination of Adherence

The period between January 1, 1998, and December 31, 1998, was defined as a washout period; patients who filled at least 1 prescription in this period were defined as previous users of statins and were excluded from further analysis. We did not include in the study patients who started statins between January 1, 2006, and December 31, 2006. For all the patients, the first month in which the patient filled a prescription was defined as the starting month. From this point, we calculated 12 months of adherence with statin treatment. We defined *adherence* as buying at least 80% of the expected number of pills over this 12-month period.[17] In this model for adherence, days off pills are not counted, but rather the 365-day pill consumption is used as a surrogate for 1-year adherence. If patients changed brand or dosage during this period, they still were considered adherent. We ran the same model defining adherence as buying at least 70% or 50% of the expected number of pills. All 3 definitions gave similar results, so we chose to present the results obtained with 80% adherence.

Adherence till the end of the study was defined as receiving treatment according to the above definition (at least 292 pills in 365 days) for the last full 12 months of follow-up. Poor adherence to treatment was defined as consumption of fewer than 292 pills in the 365 days *after* a year of adherence.

Patient Characteristics

From the HMO's central register of patients with chronic diseases,[19] we retrieved data to determine whether the patients had diabetes mellitus or cardiovascular diseases, and the date of the diagnosis. For each participant we retrieved sociodemographic data from the HMO database, including sex, place of residence, year of birth, country of origin, and year of immigration to Israel. A patient

was defined as having low socioeconomic status if he or she had an exemption from paying his monthly National Insurance contribution. Patients with low socioeconomic status have a copayment discount.

A patient was defined as a new immigrant if he or she came to Israel after 1990. We choose the year 1990 as a cutoff point because in this year (as in many of the years in the early 1990s), there was a large wave of immigrants to Israel, especially from the former Soviet Union.

The collection of data for the study was done anonymously and in conformity with all country laws and the Helsinki Declaration.

Statistical Analysis

We analyzed adherence as a continuous variable of the number of years to discontinuation based on Kaplan-Meier survival curves. Strata were compared with the log-rank test.

■ **Table 1.** Demographics and Chronic Diseases at the Beginning of Statin Treatment (N = 47,680)

Variable	No. (%)[a]
Demographics	
Age at beginning, mean ± SD, y	61.3 ± 11.8
Female	25,392 (53.3)
Country of origin and new immigration	
Israel	12,015 (25.2)
Asia and North Africa	15,117 (31.7)
Former Soviet Union and East European countries	17,620 (36.9)
West Europe and Americas	2137 (4.5)
Ethiopia	549 (1.1)
Immigration in 1990 and later	7854 (16.5)
Low socioeconomic status	14,253 (29.9)
Urban residence	38,955 (81.7)
Chronic diseases	
Before treatment	
Hypertension	12,799 (26.8)
Diabetes mellitus	7804 (16.4)
Ischemic heart disease	5358 (11.2)
Postcerebrovascular accident	1224 (2.6)
Congestive heart failure	1138 (2.4)
New cases during follow-up	
Hypertension	10,915 (22.9)
Diabetes mellitus	6335 (13.3)
Ischemic heart disease	7638 (16.0)
Postcerebrovascular accident	2467 (5.2)
Congestive heart failure	1984 (4.2)

[a] Except where indicated.

We used Cox regression models to calculate the hazard ratio (HR) for discontinuation after adjusting for patient demographic factors and chronic diseases. Stata 8 statistical software (StataCorp LP, College Station, Texas) was used for all analyses. Probabilities of less than 5% were taken to indicate statistical significance.

RESULTS

We identified 47,680 patients who met the inclusion criteria. **Table 1** shows the population characteristics at entry. The number of new patients treated with statins every year increased rapidly during the study period from 4576 new patients in 1999 to 8787 in 2005.

Adherence With Statin Treatment

Using the definition of 80% adherence, 61.1% of the patients stopped treatment during the first year. In the years to follow, treatment discontinuation continued. After 3 and 6 years, only 21.8% and 9.6% of the patients, respectively, were still on statins.

Table 2 presents the HRs of treatment discontinuation associated with potential predictors (an HR <1 means better adherence with statins compared with the reference group). The risk of discontinuation was higher in new immigrants who came to Israel after 1990 (HR = 1.20; 95% confidence interval [CI] = 1.14, 1.27) and immigrants from Ethiopia (HR = 1.22; 95% CI = 1.16, 1.29) compared with others. The adherence was higher in patients who had chronic diseases before starting statins (HR = 0.88; 95% CI = 0.84, 0.94), or when chronic disease was diagnosed during the course of treatment for hyperlipidemia (HR = 0.90; 95% CI = 0.86, 0.95).

Patients younger than age 50 or older than 79 had lower adherence rates than the other patients. Place of residence and sex had a statistically significant but a very small effect on adherence rates, while low socioeconomic status did not have any effect on adherence rates.

■ **Table 2.** Predictors of Statin Treatment Discontinuation After Adjusted Analysis (N = 47,680)

Covariate	Hazard Ratio[a] (95% CI)
Age (compared with patients age ≤ 49 y)	
50-59 y	0.83 (0.77, 0.88)
60-69 y	0.77 (0.72, 0.82)
70-79 y	0.77 (0.72, 0.82)
≥80 y	0.89 (0.81, 0.98)
Sex	
Female (compared with male)	0.95 (0.92, 0.99)
Country of origin	
Ethiopia (compared with others)	1.22 (1.16, 1.29)
New immigrants	
Immigration in 1990 and later (compared with others)	1.20 (1.14, 1.27)
Socioeconomic status	
Low socioeconomic status (compared with others)	1.02 (0.98, 1.07)
Place of residence	
Villages and small towns (compared with cities)	0.95 (0.90, 1.01)
Chronic disease [b]	
No chronic disease	1
Any chronic disease before starting statins	0.88 (0.84, 0.94)
Any chronic disease after starting statins	0.90 (0.86, 0.95)

CI indicates confidence interval.
[a]A hazard ratio of less than 1 means better adherence with statin therapy compared with the reference group.
[b]Chronic disease was defined as at least 1 of the following: ischemic heart disease, diabetes mellitus, hypertension, congestive heart failure, peripheral vascular disease, or postcerebrovascular accident.

DISCUSSION

The current study was of current routine care of community patients. We found that the number of patients beginning statins between 2003 and 2005 increased 32%. Although statins clearly have become a cornerstone in the management of cardiovascular risk, both for primary and secondary prevention, the adherence rates are very disappointing. In the vast majority of cases, statins are lifelong medications. To the best of our knowledge, this large-scale, retrospective, longitudinal study is the longest follow-up reported in a routine clinical care setting.[11,13,20] The rate of discontinuation during the first year was very high: 61.1%. This rate is much higher than that previously reported in clinical trials.[21,22] It is much higher than the 26% reported by Caspard et al[11] and similar to the 57% reported by Schultz et al[12] in routine care settings.

We were able to identify determinants of adherence to statin therapy. Adherence rates were higher for secondary prevention than for primary prevention. This finding, which was

consistent across the entire spectrum of cardiovascular risk factors that we evaluated, is not surprising and is in concordance with previous studies that had shorter follow-up periods.[7,8,12] However, even in this high-risk population, adherence rates were disappointing. We must search for better ways to increase adherence in this group of patients by educational, medical, and administrative interventions.

Sociodemographic characteristics affect adherence. Low income did not predict a lower adherence rate in our patients, possibly because of the relatively low copayment, which is even lower for low-income patients. This low copayment may be unique to the Israeli health system and not generalizable to other health systems.[7,23] However, we were able to determine other demographic characteristics of patients with low adherence. Low rates of adherence were found in new immigrants, who may have come from cultures with different health beliefs (equivalent to minorities in other studies).[7,23,24] They may have difficulties in the immigration process that influence adherence as well as many other health indicators, and we should focus on this population in this vulnerable period.

There are several strengths to our study. Use of pharmacy claims allows assessment of long-term adherence in a large population. Patients and physicians were unaware that adherence would be assessed; thus, behavior was not altered by adherence measurements, a common flaw of studies based on self-report or pill count. Our ability to link documentation of the onset of chronic diseases, accurate sociodemographic data, and pharmacy claims gave us the opportunity to eliminate possible confounders.

The study has a few limitations. The setting may not be representative of usual care in populations and health systems in other parts of the world. But the very large sample and the confounders entered into the statistical model enable readers to make the needed adaptations. We may have missed clinical correlations when we used pharmacy claims. It may be that therapy was discontinued for clinically appropriate reasons such as adverse drug events or conversion to other therapies, or because LDL-C target levels were reached by weight reduction, change in diet, and exercise. However, statins are very safe, and conversion from statins to nonstatin agents is rare.[25] The possibility that medications were stopped because patients achieved target levels of LDL-C deserves further study. There is no way to verify that those who purchased a prescription actually consumed the pills. But this surrogate fits for large epidemiologic studies.

Take-away Points

Adherence with statin therapy in a usual care setting (Israel's largest HMO) was poor.

■ The low rate of adherence in new immigrants was of particular concern.

■ The adherence rates in patients with cardiovascular diseases or with cardiovascular risk factors were higher but were still unacceptably low.

■ Our results suggest that intervention programs are needed and should target all groups of patients.

To evaluate adherence, we considered all brands and dosages together. More potent statins or a higher dosage might indicate more severe disease, and better stratification of the cohort might have resulted if these factors had been considered. However, as we are dealt with an extended follow-up period, we presumed that dosage and brand were not constant for the whole period in many patients. We chose, therefore, stratification according to primary versus secondary prevention only.

Our criterion for adherence was 1 year of at least 80% adherence, but patients who experienced breaks in statin treatment because they were out of the country or had an extended hospitalization could have been falsely labeled as discontinuers. However, in our HMO, a patient leaving the country can get 3 months of chronic medications in advance. Also, we presumed that only a small minority of the cohort had hospitalizations longer than 2 months, and only a small number of discontinuations could be explained this way.

Author Affiliations: From the Department of Family Medicine, Tel Aviv University, Tel Aviv Israel (SV, MS); and Clalit Health Services, Rishon LeZion, Israel (SV, MS, TB, AE).

Address correspondence to: Shlomo Vinker, MD, Department of Family Medicine, Tel Aviv University, POB 14238, Ashdod 77042, Israel. E-mail: vinker01@zahav.net.il.

REFERENCES

1. American Heart Association. Heart Disease and Stroke Statistics-2003 Update. Dallas, TX: American Heart Association, 2003. http://www.americanheart.org/downloadable/heart/1040391091015HDS_Stats_03.pdf. Accessed February 27, 2008.

2. Randomized trial of cholesterol lowering in 4444 patients with coronary heart disease: The Scandinavian Simvastatin Survival Study (4S). *Lancet.* 1994;344(8934):1383-1389.

3. Expert Panel on Detection Evaluation, Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Executive summary of the third report of the National Cholesterol Education Program (NCEP). *JAMA.* 2001;285(19):2486-2497.

4. Kumana CR, Cheung BMY, Lauder IJ. Gauging the impact of statins using number needed to treat. *JAMA.* 1999;282(20):1899-1901.

5. Pearson TA, Laurora I, Chu H, Kafonek S. The lipid treatment assessment project (L-TAP): a multicenter survey to evaluate the percentages of dyslipidemic patients receiving lipid-lowering therapy and achieving low-density lipoprotein cholesterol goals. *Arch Intern Med.* 2000;160(4):459-467.

6. Meyer JW, Schultz JS, O'Donnell JC, Patel PA, Sasane RM. Patterns and effectiveness of lipid-lowering therapies in a managed care environment. *Value Health.* 2005;8(5):601-612.

7. Benner JS, Glynn RJ, Mogun H, Neumann PJ, Weinstein MC, Avorn J. Long-term persistence in use of statin therapy in elderly patients. *JAMA.* 2002;288(4):455-461.

8. Jackevicius CA, Mamdani M, Tu JV. Adherence with statin therapy in elderly patients with and without acute coronary syndrome. *JAMA.* 2002;288(4):462-467.

9. Ford ES, Mokdad AH, Giles WH, Mensah GA. Serum total cholesterol concentrations and awareness, treatment, and control of hypercholesterolemia among US adults. Findings from the National Health And Nutrition Examination Survey, 1999 to 2000. *Circulation.* 2003;107(17):2185-2189.

10. Kamal-Bahl SJ, Burke T, Watson D, Wentworth C. Discontinuation of lipid modifying drugs among commercially insured United States patients in recent clinical practice. *Am J Cardiol.* 2007;99(4):530-534.

11. Caspard H, Chan AK, Walker AM. Compliance with a statin treatment in a usual care setting: retrospective database analysis over 3 years after treatment initiation in health maintenance organization enrollees with dyslipidemia. *Clin Ther.* 2005;27(10):1639-1646.

12. Schultz JS, O'Donnell JC, McDonough KL, Sasane R, Meyer J. Determinants of compliance with statin therapy and low-density lipoprotein cholesterol goal attainment in a managed care population. *Am J Manag Care.* 2005;11(5):306-312.

13. Walley T, Folino-Gallo P, Stephens P, Van Ganse E. Trends in prescribing and utilization of statins and other lipid lowering drugs across Europe 1997-2003. *Br J Clin Pharmacol.* 2005;60(5):543-551.

14. McGinnis B, Olson KL, Magid D, et al. Factors related to adherence to statin therapy. *Ann Pharmacother.* 2007;41(11):1805-1811.

15. Pedan A, Varasteh L, Schneeweiss S. Analysis of factors associated with statin adherence in a hierarchical model considering physician, pharmacy, patient, and prescription characteristics. *J Manag Care Pharm.* 2007;13(6):487-496.

16. Mann DM, Allegrante JP, Natarajan S, Halm EA, Charlson M. Predictors of adherence to statins for primary prevention. *Cardiovasc Drugs Ther.* 2007;21(4):311-316.

17. Sikka R, Xia F, Aubert RE. Estimating medication persistency using administrative claims data. *Am J Manag Care.* 2005;11(7):449-457.

18. State of Israel, Ministry of Health, Department of Health Economics. Statistical Data for the Period 1995-2007. December 2007. http://www.health.gov.il/download/pages/Health_Economics.pdf. Accessed February 27, 2008.

19. Rennert G, Peterburg Y. Prevalence of selected chronic diseases in Israel. *Isr Med Assoc J.* 2001;3(6):404-408.

20. Larsen J, Andersen M, Kragstrup J, Gram LF. High persistence of statin use in a Danish population: compliance study 1993-1998. *Br J Clin Pharmacol.* 2002;53(4):375-378.

21. Downs JR, Clearfield M, Weis S, et al, and Air Force/Texas Coronary Atherosclerosis Prevention Study. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. *JAMA.* 1998;279(20):1615-1622.

22. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,356 high-risk individuals: a randomized placebo-controlled trial. *Lancet.* 2002;360(9396):7-22.

23. Kaplan RC, Bhalodkar NC, Brown EJ Jr, White J, Brown DL. Race, ethnicity, and sociocultural characteristics predict noncompliance with lipid-lowering medications. *Prev Med.* 2004;39(6):1249-1255.

24. Williams ML, Morris MT 2nd, Ahmad U, Yousseff M, Li W, Ertel N; VANJHCS Research Group. Veterans Affairs of New Jersey Healthcare System. Racial differences in compliance with NCEP-II recommendations for secondary prevention at a Veterans Affairs medical center. *Ethn Dis.* 2002;12(1):S1-58-62.

25. Grant RW, O'Leary KM, Weilburg JB, Singer DE, Meigs JB. Impact of concurrent medication use on statin adherence and refill persistence. *Arch Intern Med.* 2004;164(21):2343-2348. ■