Adherence to Statin Therapy and LDL Cholesterol Goal Attainment by Patients With Diabetes and Dyslipidemia

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OBJECTIVE — The purpose of this study was to assess the relationship between adherence to statin therapy and LDL cholesterol goal achievement in patients with diabetes and dyslipidemia.

RESEARCH DESIGN AND METHODS — The records of patients being medically treated for dyslipidemia in a managed care diabetes program from January 2001 to December 2002 were used to assess LDL cholesterol goal attainment (<100 mg/dl) and to compute a 9-month medication possession ratio (percentage of days when medication was available [MPR], beginning with the first prescription in the database).

RESULTS — A total of 653 patient records was analyzed. The average MPR was significantly higher for men than for women (0.75 vs. 0.66, $P < 0.05$). Overall, 44% ($n = 290$) of the patients achieved an LDL cholesterol level <100 mg/dl (52% of men and 37% of women, $P < 0.05$). A significant correlation emerged between MPR and plasma LDL cholesterol ($P < 0.001$), and MPR was significantly higher in patients who achieved the LDL cholesterol target than in those who did not (0.82 vs. 0.61, $P < 0.05$).

CONCLUSIONS — Although statins are highly effective for decreasing LDL cholesterol levels in patients with dyslipidemia, including those with diabetes, failure to reach LDL cholesterol targets remains common. Adherence to statin therapy, as reflected by MPR, is closely related to LDL cholesterol goal attainment in patients with diabetes and dyslipidemia. The probability of goal achievement appears to increase substantially when the MPR is >0.80. Pharmacy records can be used to identify patients who are poorly compliant with statin therapy and at high risk for failure to attain LDL cholesterol goals. Because outcomes are directly related to patients' medication-taking behavior, when clinical goals (such as serum cholesterol levels) are not being reached, adherence should be the first item assessed by the clinician.

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More than 16 million people in the U.S. have type 1 or type 2 diabetes (1) and, as a result, are at significantly increased risk for cardiovascular disease, including coronary heart disease (CHD) (2,3). The frequent coexistence of diabetes and hypercholesterolemia further raises the risk for CHD and its associated morbidity (4). In fact, according to the Third Report of the National Cholesterol Education Program Adult Treatment Panel (NCEP ATPIII), the presence of diabetes produces a risk for coronary events equivalent to that of a history of CHD (5).

Lipid-lowering therapy, particularly with hydroxymethylglutaryl-CoA reductase inhibitors (statins), is well known to reduce cardiovascular risk across a wide range of patients (6,7), including those with CHD and diabetes or impaired fasting glucose values, as shown in a subanalysis of results from the Scandinavian Simvastatin Survival Study (8). The Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm (ASCOT-LLA) and the GREek Atorvastatin and Coronary-heart-disease Evaluation (GREACE) also demonstrated a decreased risk for CHD and related clinical events in patients with diabetes (9,10).

Despite the common occurrence of dyslipidemia in patients with diabetes, the consequent high risk for CHD, and well-publicized treatment guidelines, elevated cholesterol levels remain undertreated in this population. In one evaluation of data from a managed care organization, only 15.8% of 6,586 patients achieved their LDL cholesterol goal of <100 mg/dl (11).

The failure to achieve goals for dyslipidemia can be laid at many doors, including a lack of follow-up and improper titration of the starting statin dose (11–14), but perhaps most important is poor adherence to treatment, even by patients at high cardiovascular risk. In an analysis involving 34,501 elderly patients (23.5% with diabetes), the proportion of days covered by treatment was 79% during the first 3 months; thereafter, adherence fell dramatically to 56% after 6 months and to 42% after 120 months (12). Moreover, poor adherence to statin therapy cuts across different degrees of cardiovascular risk. Two-year adherence was 40.1% by patients prescribed a statin after an acute coronary event, 36.1% by patients with CHD, and 25.4% in patients being treated for primary prevention (15).

This study evaluated the prevalence of nonadherence to statin therapy among patients with diabetes and dyslipidemia and determined the relationship between adherence and attainment of LDL cholesterol goals. An assessment of this kind is a necessary first step for the development of

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Abbreviations: CHD, coronary heart disease; MPR, percentage of days when medication was available; NCEP ATPIII, Third Report of the National Cholesterol Education Program Adult Treatment Panel.
A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Demographic characteristics, MPR, and LDL cholesterol goal attainment*

Characteristic	Total	Men	Women
n	653	317	336
Age (years)	54.1 ± 7.8	55.2 ± 7.1*	53.0 ± 8.2*
MPR	0.70 ± 0.30	0.75 ± 0.29*	0.66 ± 0.31*
Number at LDL cholesterol goal (%)	290 (44)	165 (52)†	125 (37)†

Data are means ± SD unless otherwise noted. *$P < 0.05$ men vs. women (Student's *t* test); †$P < 0.05$ men vs. women (χ^2 test).

interventions to improve adherence to statin therapy and thus reduce cardiovascular risk.

RESEARCH DESIGN AND METHODS

— This study used information from the ~6,000 patients enrolled in the diabetes disease management program of a 188,000-member independent practice association model HMO. All statins prescribed were identified from the pharmacy claims database for the 2 years between 1 January 2001 and 31 December 2002. All LDL cholesterol measurements available from these patients over the same period were also included.

Patients without a LDL laboratory value or whose most recent LDL cholesterol measurement was before or within 30 days after the first statin prescription in the database were excluded. The remaining records were used to compute a 9-month MPR, defined as the percentage of days when medication was available, beginning with the first prescription in the database. Adherence calculations were performed with Standardized Therapy Adherence Research Tool (START, Pfizer, New York, NY) software (16). Patients were also excluded if they were first prescribed a statin after 31 March 2002 (to have a complete 9 months of therapy available for analysis). The LDL cholesterol goal for all patients was <100 mg/dl, as specified by NCEP ATPIII (5).

Student's *t* tests, χ^2 tests, and calculation of linear correlation coefficients and 95% CIs were used to evaluate results. A *P* value <0.05 was required for statistical significance in all analyses.

RESULTS

— Among the 653 patients whose records met the inclusion criteria and were analyzed, men had a significantly higher average MPR than women (Table 1). Overall, 44% ($n = 290$) of patients achieved their LDL cholesterol goal. Once again, the rate of achievement was higher among men.

MPR and LDL cholesterol goal attainment

As the MPR increased, the LDL cholesterol level declined (Fig. 1). A Pearson correlation showed a significant positive association between MPR and LDL ($r = -0.393$, $P < 0.001$).

In this study, the probability of achieving the LDL cholesterol goal rose progressively with MPR (Fig. 2). The mean MPR for the 290 patients who reached their LDL cholesterol target (0.82 ± 0.25 [95% CI 0.79−0.85]) was significantly higher ($P < 0.05$) than that (0.61 ± 0.30 [0.58−0.64]) for the 363 patients who were not at the goal by study end. Further, patients whose MPR was >0.8 had a 56–78% chance of therapeutic success; this probability decreased to 20–42% when the MPR was <0.8.

The choice of a statin appeared to have an influence on the LDL cholesterol level but not on the MPR (Table 2). Atorvastatin, the most frequently prescribed statin in this database ($n = 470$), produced a mean LDL cholesterol level of 109.07 mg/dl, the lowest level save for 108 mg/dl achieved with lovastatin, which was taken by only two patients. Other mean LDL cholesterol levels ranged from 113.26 mg/dl with simvastatin to 125.05 mg/dl with fluvastatin.

CONCLUSIONS

— Medical care for the patient with diabetes, especially medication regimens, has become more complex over time, producing a barrier to achieving evidence-based goals of treatment. The number of primary care visits that include the use of oral hypoglycemic, antihypertensive, and lipid-lowering medications in the same patient has significantly increased over the past decade (17). Such polypharmacy is a growing barrier to proper medication adherence and the attainment of treatment goals for all conditions being managed. Increasingly stringent and complicated lipid treatment goals (18,19) and the limited amount of time available during office and clinic visits to discuss the multiple aspects of this care (17) are other significant factors that currently contribute to the low implementation of published guidelines for managing dyslipidemia in diabetic patients. The consequences of poor adherence in the diabetic population are becoming clearer. A recent evaluation showed that an oral hypoglycemic medication MPR of <80% correlated with an

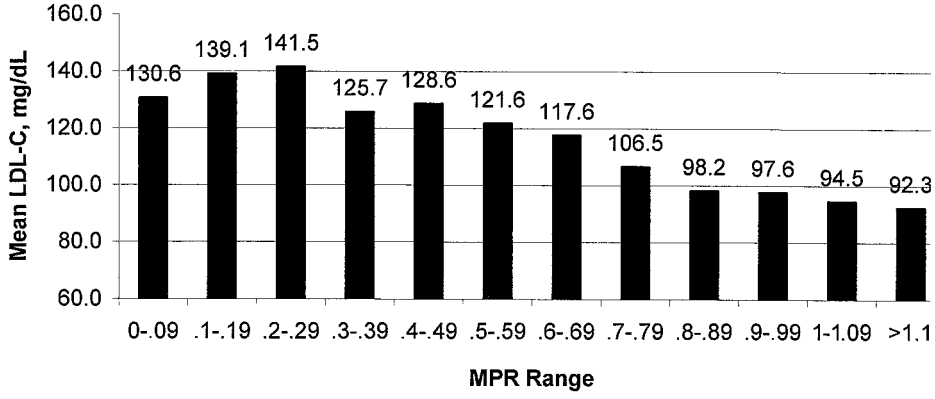

Figure 1—*Relationship between MPR range and mean LDL cholesterol level.*

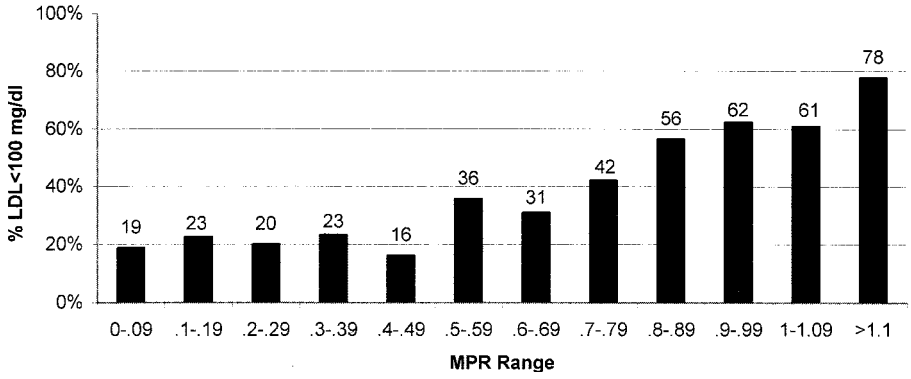

Figure 2—*Relationship between MPR range and LDL cholesterol goal attainment (<100 mg/dl).*

increased risk of hospitalization in the following year (22).

Our study using a diabetes disease management database demonstrates that adherence to statin therapy by patients with diabetes and dyslipidemia is an important determinant of LDL cholesterol reduction and goal attainment. Highlighting the relationship between MPR and LDL cholesterol goal attainment was a marked rise in the probability of successful treatment when the MPR was >0.80. Based on these findings, we have taken steps within our disease management program to have case managers assess medication adherence and potential barriers when clinical goals are not being reached. The barriers now monitored and addressed include patient knowledge and perception of therapy benefit (26,29).

The relationship between adherence to therapy and LDL cholesterol levels achieved in this study is consistent with findings from other recent reports. Among 207 consecutive patients with CHD and dyslipidemia, total cholesterol and LDL cholesterol levels were lower and HDL cholesterol levels higher in compliant than in noncompliant patients treated with statins (20).

Poor adherence to statin therapy and failure to achieve LDL cholesterol goals amplify the significant morbidity and mortality already present in patients with dyslipidemia. In one evaluation of 5,590 patients who had an incident myocardial infarction and at least one additional attack, the risks for recurrence and mortality were lower in patients who adhered to statin therapy than in those who did not (23). The proven effectiveness of statins in bringing adherent patients to the LDL cholesterol goal suggests that nonadherence should be strongly suspected when goals are not achieved and that barriers to adherence should be immediately investigated. Among the potential obstacles to adherence are nonwhite race, low income, old age, psychiatric illness (depression, dementia), the occurrence of CHD events during therapy, smoking, comorbid hypertension, and substance abuse, although these have been determined to be inconsistently correlated with adherence (12,24,25). One of the limitations of our study, it should be pointed out, was the absence of more detailed demographic information, which may or may not have provided greater insight into why poor adherence occurred; however, our goal was focused on the relationship between adherence and goal attainment in this population.

The 44% of patients who reached their LDL cholesterol goal in the present analysis is somewhat higher than that reported in previous surveys. Overall, only 38% of patients achieved NCEP ATPIII–specified LDL cholesterol target levels in the Lipid Treatment Assessment Project (L-TAP)—68% of low-risk patients, 37% of high-risk patients, and only 18% of patients with CHD (21). In an analysis of 6,586 patients with diabetes who were members of a single managed care organization, only 15.8% demonstrated LDL cholesterol levels <100 mg/dl (11). The present results must be compared cautiously with those from other studies because of the relatively short (9-month) period in this evaluation and the known decline in adherence to statin therapy over time (12). Possible explanations for the higher LDL goal attainment may include the impact of the disease management program and differences in adherence rates.

Looking forward, attempts to enhance adherence will require a multifaceted, comprehensive, and empathetic approach (25,26). Central to any such efforts are education about the importance of controlling dyslipidemia, clear instructions on dosing, continued interaction between patient and health care professionals, implementation of strategies to overcome high drug costs, adverse effect evaluation and management, and integration of statins with other medications, including use of a daily pill organizer (27). The mutual establishment of clinical goals between the health care provider and the patient, along with frequent follow-up on these goals, are also important for improving adherence (28). We also believe

Table 2—*LDL cholesterol MPR values for different statins used*

Statin	No. of patients*	Mean LDL cholesterol (mg/dl)	Mean 9-month MPR
Atorvastatin	470	109.07	0.71
Pravastatin	161	114.86	0.70
Simvastatin	128	113.26	0.69
Cerivastatin†	41	122.83	0.62
Fluvastatin	19	125.05	0.70
Lovastatin	2	108.00	0.86

*Patients taking more than one statin were counted in each statin calculation. There was no statistically significant difference in mean LDL or MPR between the three most frequently used statins; †now withdrawn from the market.

that a stronger message about the benefits of medicine is needed and should be incorporated into patient counseling, because patients who believe in the necessity of a particular medication are more likely to be adherent (29). For example, the patient perception that statins primarily "lower cholesterol" should be replaced with an emphasis on the "prevention of heart attack and stroke."

Adherence to statin therapy, as reflected by the MPR, is closely related to LDL cholesterol goal attainment by patients with diabetes and dyslipidemia, with the probability of success appearing to increase substantially when the MPR is >0.80. In this database, adherence to therapy and goal achievement is higher among men than among women. This study also demonstrates the usefulness of pharmacy records in identifying patients at increased risk of failure to attain LDL cholesterol goals with statins (by calculation of the MPR). Because outcomes are directly related to patients' medication-taking behavior, adherence should be the first item assessed when clinical goals (such as serum cholesterol levels) are not being reached.

References

1. American Heart Association: *Heart Disease and Stroke Statistics: 2003 Update*. Dallas, TX, American Heart Association, 2003
2. Stamler J, Vaccaro O, Neaton JD, Wentworth D: Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. *Diabetes Care* 16:434–444, 1993
3. Grundy SM, Pasternak R, Greenland P, Smith S Jr, Fuster V: Assessment of cardiovascular risk by use of multiple-risk-factor assessment equations: a statement for healthcare professionals from the American Heart Association and the American College of Cardiology. *Circulation* 100:1481–1492, 1999
4. Grundy SM, Balady GJ, Criqui MH, Fletcher G, Greenland P, Hiratzka LF, Houston-Miller N, Kris-Etherton P, Krumholz HM, LaRosa J, Ockene IS, Pearson TA, Reed J, Washington R, Smith SC Jr: Primary prevention of coronary heart disease: guidance from Framingham: a statement for healthcare professionals from the AHA Task Force on Risk Reduction. *Circulation* 97:1876–1887, 1998
5. Expert Panel on Detection, Evaluation, and 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* 285:2486–2497, 2001
6. Eisenberg DA: Cholesterol lowering in the management of coronary artery disease: the clinical implications of recent trials. *Am J Med* 104 (Suppl. 2A):2S–5S, 1998
7. Teo KK, Burton JR: Who should receive HMG CoA reductase inhibitors? *Drugs* 62: 1707–1715, 2002
8. Haffner SM, Alexander CM, Cook TJ, Boccuzzi SJ, Musliner TA, Pedersen TR, Kjekshus J, Pyorala K: Reduced coronary events in simvastatin-treated patients with coronary heart disease and diabetes or impaired fasting glucose levels: subgroup analyses in the Scandinavian Simvastatin Survival Study. *Arch Intern Med* 159:2661–2667, 1999
9. Sever PS, Dahlof B, Poulter NR, Wedel H, Beevers G, Caulfield M, Collins R, Kjeldsen SE, Kristinsson A, McInnes GT, Mehlsen J, Nieminen M, O'Brien E, Ostergren J, ASCOT Investigators: Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. *Lancet* 361:1149–1158, 2003
10. Athyros VG, Papageorgiou AA, Mercouris BR, Athyrou VV, Symeonidis AN, Basayannis EO, Demitriadis DS, Kontopoulos AG: Treatment with atorvastatin to the National Cholesterol Educational Program goal versus 'usual' care in secondary coronary heart disease prevention: the GREek Atorvastatin and Coronary-heart-disease Evaluation (GREACE) study. *Curr Med Res Opin* 18:220–228, 2002
11. Straka RJ, Taheri R, Cooper SL, Tan AWH, Smith JC: Assessment of hypercholesterolemia control in a managed care organization. *Pharmacotherapy* 21:818–827, 2001
12. Benner JS, Glynn RJ, Mogun H, Neumann PJ, Weinstein MC, Avorn J: Long-term persistence in use of statin therapy in elderly patients. *JAMA* 288:455–461, 2002
13. Cozma LS, Ogunko A, Rees A: Secondary prevention of hypercholesterolaemia: results of an audit conducted in South Wales (Abstract). *Heart* 84:E3, 2000
14. Svilaas A, Risberg K, Thoresen M, Ose L: Lipid treatment goals achieved in patients treated with statin drugs in Norwegian general practice. *Am J Cardiol* 86:1250–1253, 2000
15. Jackevicius CA, Mamdani M, Tu JV: Adherence with statin therapy in elderly patients with and without acute coronary syndromes. *JAMA* 288:462–467, 2002
16. Day D: Use of pharmacy claims databases to determine rates of medication adherence. *Adv Ther* 20:164–176, 2003
17. Grant RW, Pirraglia PA, Meigs JB, Singer DE: Trends in complexity of diabetes care in the United States from 1991 to 2000. *Arch Intern Med* 164:1134–1139, 2004
18. Grundy SM, Cleeman JI, Merz CN, Brewer HB Jr, Clark LT, Hunninghake DB, Pasternak RC, Smith SC Jr, Stone NJ, National Heart, Lung, and Blood Institute, American College of Cardiology Foundation, American Heart Association: Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation* 110:227–239, 2004
19. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III): Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation* 106:3143–3421, 2002
20. Mansur AP, Mattar APL, Tsubo CE, Simão DT, Yoshi FR, Daci K: Prescription and adherence to statins of patients with coronary artery disease and hypercholesterolemia. *Arq Bras Cardiol* 76:115–118, 2001
21. 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* 160:459–467, 2000
22. Lau DT, Nau DP: Oral antihyperglycemic medication nonadherence and subsequent hospitalization among individuals with type 2 diabetes. *Diabetes Care* 27: 2149–2153, 2004
23. Wei L, Wang J, Thompson P, Wong S, Struthers AD, MacDonald TM: Adherence to statin treatment and readmission of patients after myocardial infarction: a six year follow up study. *Heart* 88:229–233, 2002
24. Kopjar B, Sales AEB, Piñeros SL, Sun H, Li Y-F, Hedeen AN: Adherence with statin therapy in secondary prevention of coronary heart disease in Veterans Administration male population. *Am J Cardiol* 92: 1106–1108, 2003
25. Vermeire E, Hearnshaw H, Van Royen P, Denekens J: Patient adherence to treatment: three decades of research: a comprehensive review. *J Clin Pharmacol Ther* 26:331–342, 2001
26. Krueger KP, Felkey BG, Berger BA: Improving adherence and persistence: a review and assessment of interventions and description of steps toward a national ad-

herence initiative. *J Am Pharm Assoc* 43: 668–679, 2003
27. LaRosa JH, LaRosa JC: Enhancing drug compliance in lipid-lowering treatment. *Arch Fam Med* 9:1169–1175, 2000
28. Miller NH, Hill M, Kottke T, Ockene IS, Expert Panel on Compliance: The multilevel compliance challenge: recommendations for a call to action: a statement for healthcare professionals. *Circulation* 95: 1085–1090, 1997
29. Ross S, Walker A, MacLeod MJ: Patient compliance in hypertension: role of illness perceptions and treatment beliefs. *J Hum Hypertens* 18:607–613, 2004