Relative Effectiveness of Niacin and Lovastatin for Treatment of Dyslipidemias in a Health Maintenance Organization

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BACKGROUND. We conducted an historical cohort study to evaluate the relative effectiveness of niacin and lovastatin in the treatment of dyslipidemias in patients enrolled in a health maintenance organization (HMO).

METHODS. To be eligible for this study, adults aged 18 years and older who were initially treated with either niacin or lovastatin between January 1, 1992, and December 31, 1993, were identified from pharmacy databases. Each potentially eligible member with a fasting lipid panel prior to initiation of drug therapy and with a second fasting lipid panel between 9 and 15 months after initiation of drug therapy was included in the study. A total of 244 patients treated with niacin and 160 patients treated with lovastatin had complete data and are the subjects of this report.

RESULTS. Patients initially treated with lovastatin had higher baseline mean cholesterol and low-density lipoprotein (LDL) levels as well as higher rates of diabetes mellitus and heart disease than did patients initially treated with niacin. Lovastatin use was associated with a mean 25.8% decrease in LDL cholesterol, while niacin use was associated with a mean 17.5% drop in LDL cholesterol (t=3.19, P <.002). Niacin use was associated with a 16.3% improvement in high-density lipoprotein (HDL) cholesterol, while HDL-cholesterol levels in the lovastatin group improved 1.5% (t=4.74, P <.001). Niacin use was associated with an 18.4% improvement in triglycerides, while lovastatin use was associated with an 8% improvement in triglyceride levels (t=2.81, P=.005). Differences in LDL/HDL ratio from before treatment to follow-up were no different in the two groups of patients (t=-1.21, P=.22). A total of 46% of patients initially treated with either drug reached their treatment goals in accordance with those set by the National Cholesterol Education Program. Drug discontinuation rates were 73% for niacin and 52% for lovastatin at follow-up, which averaged 10.7 months in each group.

CONCLUSIONS. These results suggest that both niacin and lovastatin are effective in treating dyslipidemic patients in this care system, and that physicians appropriately use lovastatin more often for patients with higher baseline LDL levels and more comorbidity. The data also strongly suggest that establishing an organized, population-based approach to systematically identify, treat, and monitor patients with dyslipidemias may be the single most important intervention HMOs should consider for improving control of dyslipidemias on a population basis.

KEY WORDS. Dyslipidemia; health maintenance organization; niacin; lovastatin; outcomes research. *(J Fam Pract 1997; 44:462-467)*

Recent data convincingly demonstrate that correction of dyslipidemias leads to lower rates of fatal and nonfatal myocardial infarction, cerebrovascular events, and death.[1-3] Recent guidelines published by several expert panels give specific recommendations on how to identify and treat dyslipidemias and define treatment goals for various patients with dyslipidemias.[4-6]

Many drugs are available for treatment of dyslipidemias in adults, and published guidelines allow practitioners considerable freedom in selecting among these drugs. Niacin and the HMG-CoA reductase inhibitor lovastatin are both effective in lowering low-density lipoprotein (LDL) cholesterol but differ significantly in their mechanism of action, dosing, and cost.[7,8] We conducted an historical cohort study to compare the use and effectiveness of niacin

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and lovastatin in dyslipidemic patients enrolled in a large health maintenance organization (HMO).

METHODS

This study was conducted at a 240,000-member HMO in the Midwest. Members received their care at one of 19 staff model clinics and were referred as needed for care of dyslipidemias to a lipid clinic directed by an endocrinologist and staffed by nutritionists and pharmacists. Referral to the lipid clinic involved subspecialty assessment and development of a treatment plan. The patients were then generally returned to the care of their primary physician.

Computerized pharmacy records were used to identify HMO members over 18 years old who received initial treatment with either niacin or lovastatin at any time between January 1, 1992, and December 31, 1993. Any member who filled his or her prescription at an HMO pharmacy was identified. Not all prescriptions were filled in these pharmacies since some members over age 65 did not have drug coverage and many of these chose to fill their prescriptions elsewhere. Niacin does not require a prescription and can be obtained from a variety of sources, although it is also available at HMO pharmacies at competitive prices.

After members receiving initial treatment with lovastatin or niacin were identified from HMO pharmacy files, the medical records of these patients were reviewed. Members were included in the study only if they met all the following criteria:

1. The subject was continuously enrolled in the HMO and had received a prescription for either niacin or lovastatin between January 1, 1992, and December 31, 1993.
2. The subject had a fasting lipid panel that included cholesterol, HDL cholesterol, triglyceride, and calculated LDL cholesterol values as baseline before the initiation of the study drug.
3. The subject then had a second fasting lipid panel done between 9 and 15 months after initiation of the study drug.

There was no requirement that the member still be taking the study drug at the time of the follow-up lipid panel, since continuation of therapy and use of additional lipid-lowering agents were study outcomes of interest.

For each eligible member, a study period was defined from the date of initiation of treatment with the study drug to the date of a follow-up lipid panel 9 to 15 months later. If multiple lipid panels were done, the one done closest to the 12-month follow-up was selected. During the study period, all lipid panels from the 19 study clinics were done at one central, licensed clinical chemistry laboratory using a standard lipid assay method for total cholesterol, HDL cholesterol, and triglycerides, with LDL cholesterol being calculated and not directly assayed. Specimens for fasting lipid profiles were accepted only if a 12-hour minimum fast was documented by laboratory personnel at the time of phlebotomy.

Data for analysis were obtained from medical record audits and included sex, date of birth, dates on which niacin, lovastatin, probucol, cholestyramine, gemfibrozil, or estrogens were started and stopped. (Lovastatin was the only HMG-CoA reductase inhibitor on the formulary before 1994.) Also noted was use of any other drugs known to affect lipids, dates and values from all lipid panels during the study period, dates of all inpatient and outpatient encounters, and reason for stopping niacin or lovastatin, if available. Data on cardiovascular risk factors, including the diagnosis of coronary artery disease, cerebrovascular disease, or peripheral vascular disease, family history of heart disease, hypertension, diabetes, smoking, and other comorbid conditions were also obtained.

The data were then entered into an SAS database, reviewed for outliers or implausible values, and analyzed using SAS statistical software programs at HealthPartners Group Health Foundation. Parallel analyses of the original SAS database were conducted by USHH Outcomes Research and Management at Merck & Co, Inc, for verification.

Between January 1, 1992, and December 31, 1993, pharmacy files identified 721 members who had a prescription for niacin. Of these, 244 (34%) met the eligibility requirements outlined above. Of 670 members who had a prescription for lovastatin during the same time interval, 160 (24%) met eligibility requirements. Most excluded patients were ineligible because they had no follow-up lipid panel within the 9- to 15-month period required for this study, or because they were taking another lipid-lowering agent (most often gemfibrozil) at the time niacin or lovastatin was first prescribed.

Eligible patients included in either the niacin or

the lovastatin drug group remained in that group for the main analysis. Subgroup results are reported for patients who were and were not taking the original drug at follow-up lipid panel, for patients who were and were not subsequently treated with additional major lipid drugs, and for patients with different LDL goal levels due to differences in cardiovascular risk-factor profiles.

Bivariate analysis was done using the chi-square statistic or *t* tests, depending on the nature of the variables being evaluated. Least-squares linear regression and ANCOVA modeling of the data were then done to adjust for age, sex, baseline dyslipidemia, use of other lipid-lowering drugs, and continuation or discontinuation of the study drug.[9]

RESULTS

Table 1 shows the demographic and clinical characteristics of the patients initially treated with niacin and lovastatin. Of patients treated with lovastatin, 57% were men, while 54% of patients treated with niacin were women. Mean age of the two groups was similar but more members of the lovastatin group (39.9%) than the niacin group (30.2%) had received diagnoses of coronary artery disease. As expected, there were more patients with diabetes mellitus in the lovastatin group (18.5%) than in the niacin group (4.1%), since diabetes is a relative contraindication to the use of niacin.

Duration of follow-up averaged 10.7 months in both groups. In the group of patients initially treated with niacin, 10.1% had also received lovastatin and 43.1% had also received estrogens, probucol, cholestyramine, or gemfibrozil during the follow-up period. In the group of patients initially treated with lovastatin, 4.7% had also received niacin and 33.5% had also received estrogens, probucol, cholestyramine, or gemfibrozil during the follow-up period. Based on the relatively high proportion of patients treated with more than one lipid-lowering agent, it seems that both groups were treated quite intensively, with multidrug regimens often used to improve control of dyslipidemias. The lovastatin group had patients with more comorbid conditions, received more subspecialist care, and had more hospital admissions than the niacin group, as would have been expected owing to the higher rate of comorbidity.

Table 2 shows the changes in mean values of total cholesterol, triglycerides, HDL cholesterol, and LDL cholesterol in the two groups of patients. Lovastatin use was associated with greater drop in LDL cholesterol than niacin use (t=3.19, P <.002). Niacin use, however, was associated with greater improvement in HDL cholesterol (t=4.74, P <.001) and triglycerides (t=2.81, P=.005). The change in LDL/HDL ratio from before treatment to follow-up was not significantly different between the two groups (t= -1.21, P=.22).

Least-squares general linear models were constructed to assess the impact of age, sex, and continuation as opposed to discontinuation of the study drug on the observed bivariate associations of niacin and lovastatin with lipid levels. The bivariate associations were not changed after adjusting for these variables. Lovastatin was still associated with lower total cholesterol (F=4.31, P=.04) and with lower LDL cholesterol (F=7.43, P=.007). Niacin was still associated with better HDL cholesterol (F=18.08, P <.001), and with lower triglyceride levels (F=7.61, P=.006). The change in LDL/HDL ratio was no different in the two groups (F=1.09, P=.30). When baseline LDL-cholesterol values were added to the LDL-cholesterol model, the baseline LDL-cholesterol value was more strongly related to the follow-up LDL-cholesterol

TABLE 1

Comparison of Demographic and Medical Characteristics of the Two Study Groups

Characteristic	Niacin Group (n=248)	Lovastatin Group (n=170)
Male, %	46.4	56.9
Age, y (mean)	57.8	57.1
Coronary heart disease, %	30.2	39.9
Stroke, %	5.7	9.6
Peripheral vascular disease, %	5.3	8.4
Family history of heart disease, %	14.4	13.2
Currently smoking, %	11.7	17.9
Diabetes mellitus, %	4.1	18.5
Hypertension, %	44.5	51.2

TABLE 2

Lipid Values at Baseline and Follow-up for Patients Initially Treated with Niacin or Lovastatin

Test	N	Mean Baseline	SD	N	Mean Follow-up	SD	N	DIFF	SD	% Improvement
					NIACIN					
CHOL	238	277	36.7	240	247	47.8	237	30.1	41.8	12.4
TRIG	237	204	88.0	238	166	78.6	235	37.6	78.5	18.4
HDL	236	49.7	14.5	238	58.0	18.3	234	8.1	12.7	16.3
LDL	230	187	37.7	235	153	36.6	230	32.7	37.6	17.5
					LOVASTATIN					
CHOL	166	291	48.4	165	238	40.9	159	54.9	40.0	18.8
TRIG	160	199	84.0	163	183	79.4	157	15.	71.2	8.0
HDL	162	48.0	11.6	165	48.6	12.5	161	0.7	9.0	1.5
LDL	159	204	44.7	160	153	38.0	153	52.7	37.7	25.8

DIFF denotes differential; CHOL, cholesterol, TRIG, triglycerides; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

value (F=220.3, P <.001) than was the drug used for treatment (F=10.4, P=.001]), with model R^2=0.24.

The percent improvement in LDL cholesterol among those still taking the drug at follow-up was 17.5% for niacin and 25.8% for lovastatin. The percent improvement in LDL cholesterol among those no longer taking the drug at 1 year (but possibly taking other drugs instead) was 14.4% for those in the niacin group and 23.1% for those in the lovastatin group. ANCOVA was used to further consider the influence of concurrent use of other lipid drugs. In these models, after control for baseline lipid levels, the associations of lovastatin with more improvement in LDL-cholesterol levels (P=.002) and niacin with more improvement in HDL-cholesterol levels (P <.001) persisted.

Among study subjects, 79 of 166 (48%) of those initially treated with lovastatin were still taking the drug at follow-up, while 64 of 241 (27%) of those initially treated with niacin were still taking the drug at follow-up (χ^2=19.08, 1 *df*, $P < .001$). Baseline severity of dyslipidemia was not related to likelihood of still being treated with the study drug at follow-up.

Differences in the baseline LDL-cholesterol levels of patients treated with niacin and lovastatin are shown in Table 2. These differences were statistically significant at baseline (t=-2.95, P=.003), but not at follow-up (t=0.59, P=.56).

Finally, analyses were performed to evaluate what proportion of patients in each group did and did not achieve their target LDL goals, which were individually calculated on the basis of their risk-factor profiles and criteria put forth in the first report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (NCEP ATP I).[4] In this analysis, 46% of patients treated initially with niacin and 46% of patients initially treated with lovastatin reached their target LDL goals at follow-up. The proportion of patients reaching their goal LDL level of 130 mg/dL was 38% for lovastatin and 27% for niacin. The proportion of patients reaching their goal LDL level of 160 mg/dL was 57% for lovastatin and 61% for niacin (Table 3).

DISCUSSION

The data presented in this study show that niacin and lovastatin were used in different ways for the treatment of dyslipidemias in this HMO population. Lovastatin was significantly more effective than niacin in lowering LDL cholesterol, and was appropriately used for patients with higher baseline LDL levels, coronary artery disease, and more heart dis-

ease risk factors. Niacin was significantly more effective than lovastatin in reducing triglycerides and improving HDL cholesterol, and was used in patients with lower baseline comorbidity and less severe baseline LDL elevations. Although patients treated with lovastatin had significantly higher baseline LDL-cholesterol levels, similar proportions of patients reached their target LDL levels in both treatment groups (Table 3).

Recent data suggest that patients with and without established coronary artery disease may have decreased rates of myocardial infarction and death with effective control of dyslipidemias.[1-3] However, only 46% of patients in each of this study's drug treatment groups met the treatment goals set by the first NCEP-ATP report. If the goals set by the second NCEP-ATP report[5] were applied retrospectively to the same cases, the proportion of patients reaching goal LDL-cholesterol levels would be even lower. These data suggest two strategies HMOs could use for control of dyslipidemias on a population basis in response to recent data suggesting benefit from more widespread and more aggressive treatment of dyslipidemias.

The first strategy is for HMOs to systematically identify and track members with dyslipidemias and other cardiac risk factors such as hypertension, diabetes, and pre-existing heart disease.[10-13] Over one half of patients for whom lipid drugs were recently prescribed were excluded from this study because they had no follow-up lipid panels within 9 to 15 months; among those who did have a follow-up lipid panel, only 46% had met their lipid goals after nearly a year of follow-up. While the high rate of loss to follow-up could be interpreted as a threat to the internal validity of this study, for most patients who started taking lipid drugs there was no systematic clinical evaluation of the impact of the drug on outcomes. This observation underscores the importance of an organized system of care that is capable of identifying, monitoring, and following up such patients.

Many HMOs are able to identify dyslipidemic members using computerized laboratory and pharmacy databases. An organized, population-based approach to systematically educate, monitor, and treat dyslipidemic patients could improve both clinical outcomes and long-term costs,[13,14] and could be driven in part by sophisticated clinical databases and interdisciplinary clinical care teams based either inside or outside the clinics. While further investigation of the effectiveness of this strategy is required, it is entirely plausible that effective *organization of care* may influence lipid outcomes more than the choice of drug does, when the problem of dyslipidemias is considered on a population basis. The magnitude of the improvement that is possible on a population basis is well documented in these data.

A second area for HMOs to evaluate is drug selection. In our study, physicians often selected an HMG-CoA reductase inhibitor such as lovastatin for patients with established coronary artery disease or with very high baseline LDL levels. For patients with less severe baseline LDL elevations, less expensive agents such as niacin were often selected when education and dietary changes proved inadequate. Combination lipid drug therapy can also be considered for selected patients. Combination therapy may increase the effectiveness of lipid treatment and lower the cost of treatment, and the safety of combination therapy has received considerable support,[15-18] perhaps because lower doses of one or both drugs are often used.

The high drug discontinuation rates suggest that effective strategies to educate and follow up patients treated pharmacologically for dyslipidemias is a critically important aspect of care. The drug discontinuation rates in this study were 73% for niacin and 52% for lovastatin. One-year drug discontinuation rates reported in another managed care population were 45% for niacin and 13% for lovastatin.[19] One-year drug discon-

TABLE 3

Proportion of Patients Initially Treated with Lovastatin or Niacin Who Had Achieved Their LDL-Cholesterol Treatment Goals at Follow-up

Goal/Drug	No. of Subjects Who Achieved Goal	No. of Subjects Who Did Not Achieve Goal
Target LDL=130 mg/dL*		
Niacin	30	80
Lovastatin	35	58
Target LDL=160 mg/dL†		
Niacin	80	50
Lovastatin	42	31

*χ^2=2.48; P =.11.
†χ^2=0.31; P=.57.

tinuation rates as low as 4% for niacin[20] and 16% for lovastatin[21] have been reported in other published reports. It is likely that this is the key care element that might lead to an increase in the proportion of dyslipidemic patients reaching their target lipid levels in the future.

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