Cost-Effectiveness Analysis of Simvastatin and Lovastatin/Extended-Release Niacin to Achieve LDL and HDL Goal Using NHANES Data

EDWARD P. ARMSTRONG, PharmD; WOODIE M. ZACHRY III, PhD; and DANIEL C. MALONE, PhD

ABSTRACT

OBJECTIVE: The Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, Adult Treatment Panel III (ATP III) encouraged reduced low-density lipoprotein (LDL) cholesterol levels for a greater number of patients and reemphasized the benefits of high-density lipoprotein (HDL) cholesterol. The purpose of this study was to compare 2 regimens achieving simultaneous LDL and HDL goals.

METHODS: A decision-analytic model compared the cost-effectiveness of simvastatin and lovastatin/extended-release niacin. The perspective of the analysis was that of a health system. Product labeling was used to determine changes in cholesterol concentrations and frequencies of clinically important adverse events. The Third National Health and Nutrition Examination Survey (NHANES III) adult data were used for baseline cholesterol levels. Each product was titrated to achieve LDL and HDL goals unless an adverse effect occurred. Direct medical costs were determined for each treatment to determine cost-effectiveness.

RESULTS: For both the 130 mg/dL and 100 mg/dL LDL goal analyses (and HDL ≥ 40 mg/dL), lovastatin/extended-release niacin had higher success rates and lower estimated direct-medical costs than simvastatin. Simvastatin had the highest success rate in achieving LDL level < 160 mg/dL and HDL ≥ 40 mg/dL; however, its estimated direct-medical cost was approximately twice that of lovastatin/extended-release niacin (\$665 versus \$333).

CONCLUSION: For the LDL goals < 130 mg/dL and < 100 mg/dL (and HDL ≥ 40 mg/dL) required of the majority of U.S. residents, lovastatin/extended-release niacin was both more successful and less costly than simvastatin.

KEYWORDS: Cholesterol, ATP III, LDL, HDL, Niacin, Lovastatin, Simvastatin

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Authors

EDWARD P. ARMSTRONG, PharmD, is associate professor, and DANIEL C. MALONE, PhD, is associate professor, Department of Pharmacy Practice and Science, Center for Health Outcomes and Pharmacoeconomic Research, College of Pharmacy, University of Arizona, Tucson; WOODIE M. ZACHRY III, PhD, is an outcomes liaison, Eli Lilly and Company, Indianapolis, Indiana. (At the time of this study, Zachry was an assistant professor at the University of Arizona.)

AUTHOR CORRESPONDENCE: Edward P. Armstrong, PharmD, Associate Professor, College of Pharmacy, University of Arizona, Tucson, AZ 85721.

Tel: (520) 626-5764; Fax: (520) 626-2023;

E-mail: armstrong@pharmacy.arizona.edu

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The treatment of dyslipidemia is of tremendous importance to patients, clinicians, and health systems.¹⁻³ New cholesterol guidelines—the Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, Adult Treatment Panel III (ATP III)—have created treatment challenges by encouraging reduced low-density lipoprotein (LDL) cholesterol levels for a greater number of patients.⁴ These guidelines have also reemphasized that a low level of high-density lipoprotein (HDL) cholesterol is a major risk factor for coronary heart disease (CHD) events.⁵

This recommendation is supported by the Veterans Affairs High-Density Lipoprotein Intervention Trial (VA-HIT) that was conducted to determine whether drug therapy to increase HDL levels would decrease the incidence of major CHD events in patients with CHD and low LDL levels.^{6,7} During a median follow-up of 5.1 years, this study demonstrated that CHD events were significantly reduced in the patients who received gemfibrozil therapy when the predominant lipid abnormality was low HDL level. The HDL-Atherosclerosis Treatment Study (HATS) also supports aspects of this finding.⁸ The HATS study compared simvastatin-niacin and antioxidant-vitamin therapy, alone and together or placebo, in patients with coronary disease and low plasma levels of HDL. The HATS study found that simvastatin plus niacin provided marked clinical and angiographically measurable benefits in patients with coronary disease and low HDL levels.

The 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor regimens, commonly referred to as “statins,” have become the standard treatment to achieve lower LDL concentrations.^{1,4} This product class has been shown to be quite effective and safe in lowering LDL levels and provides a modest improvement in HDL concentrations.⁹ In addition, niacin is an established product that has been demonstrated to raise HDL levels along with lowering LDL concentrations.¹⁰ However, flushing associated with immediate-release formulations of niacin has limited its adoption as a common therapy. The availability of an extended-release formulation of niacin with reduced occurrence of adverse events, along with the ATP III emphasis on the role of HDL, has renewed interest in niacin's role in improving both LDL and HDL levels.¹¹⁻¹³ When niacin is utilized, it is often added to a statin regimen that has not achieved LDL and HDL goals as monotherapy.¹⁴⁻¹⁶

Simvastatin is an established statin product that has been used in several pivotal dyslipidemia studies. It has demonstrated efficacy in reducing overall deaths (0.7 relative risk), coronary deaths (0.58 relative risk), and the risk of undergoing

TABLE 1 Lipid Changes From Baseline

Medication	LDL Change (% Change From Baseline)	HDL Change (% Change From Baseline)
Simvastatin 20 mg ¹⁹	-38	+8
Simvastatin 40 mg ¹⁹	-41	+9
Simvastatin 80 mg ¹⁹	-47	+8
Lovastatin 20 mg/extended-release niacin 500 mg ²⁶	-25	+11
Lovastatin 20 mg/extended-release niacin 1,000 mg ²²	-30	+20
Lovastatin 40 mg/extended-release niacin 1,000 mg ²²	-36	+20
Lovastatin 40 mg/extended-release niacin 1,500 mg ²²	-37	+27
Lovastatin 40 mg/extended-release niacin 2,000 mg ²²	-42	+30

LDL = low-density lipoprotein cholesterol.

HDL = high-density lipoprotein cholesterol.

myocardial revascularization procedures (37% reduction) as noted in the Scandinavian Simvastatin Survival Study (4S).¹⁷ The Heart Protection Study found that the addition of simvastatin reduced the rates of myocardial infarction, stroke, and revascularization procedures by about 25%.¹⁸ In addition, the HATS study found significant beneficial effects with simvastatin plus niacin.⁸

The purpose of this study was to investigate the likelihood of achieving both LDL and HDL goals in the prevention of cardiovascular disease using a broad sample of U.S. residents by comparing simvastatin (Zocor) with a combined regimen of lovastatin/extended-release niacin (Advicor). An additional objective was to estimate the cost-effectiveness of each product and the incremental cost-effectiveness ratio between regimens.

Methods

Overview of Models

Decision-analytic models were created to compare the cost-effectiveness between simvastatin and lovastatin/extended-release niacin. The perspective of the analysis was that of a health system (e.g., a managed care organization). Simvastatin was selected because it has true clinical outcomes data available with its use. Publication of the 4S and HATS studies was crucial to support its inclusion in the model. The simvastatin pathway started with 20 mg per day and was titrated monthly to a maximum dosage of 80 mg per day. The lovastatin/extended-release niacin pathway started with 20 mg/500 mg per day and was titrated monthly to a maximum dosage of 40 mg/2,000 mg per day. Patients in either treatment pathway were titrated to maximum dosage unless ATP III-designated LDL and HDL targets

were realized or major side effects (myopathy, liver toxicity, or major flushing) were experienced (Figure 1). Manuscripts cited in the product package labeling were used to estimate the change in cholesterol concentrations (LDL and HDL) and the frequency of clinically important adverse events with each regimen.^{17,19-24}

Three separate models were created for the different patient populations that required LDL goals of <160 mg/dL, <130 mg/dL, or <100 mg/dL. For each decision tree, the model incorporated the titration scenarios for the changes in LDL and HDL concentrations with each dosage increase. The side-effect frequencies for each product were also included as indicated in the product labeling during the dosage titration. The model defined the effectiveness rate (i.e., successfully treated patient) as a patient achieving LDL and HDL goals and not experiencing a significant adverse event. Health care resource units and their respective costs were estimated for each pathway in the model. Cost-effectiveness was calculated by determining the direct-medical costs to achieve a successfully treated patient. The decision-analytic model framework is summarized in Figure 1.

Model Specifications

Cholesterol levels for the U.S. population were obtained from the Third National Health and Nutrition Examination Survey (NHANES III) 1988-1994 adult data file, a publicly available sample of health care information for U.S. residents from the National Center for Health Statistics and the Centers for Disease Control and Prevention.²⁵ This database was designed to provide national estimates of the health and nutritional status of the U.S.'s civilian, noninstitutionalized population. Data elements relevant to this study included patient-level data on cholesterol levels, smoking history, presence of CHD, presence of diabetes mellitus, age, and gender. These data fields were applied to the ATP III guidelines to estimate each patient's estimated 10-year CHD risk.⁴ Within the ATP III major risk factors (exclusive of LDL) that modify LDL goals, the only data element not included in the data set was the presence or absence of a family history of premature CHD. Following the ATP III framework, patients with CHD or a CHD risk equivalent (10-year CHD risk >20%) were assigned an LDL goal of <100 mg/dL. Patients with multiple (2 or more) risk factors and an estimated risk ≤20% (using the Framingham risk assessment tool) were assigned an LDL goal of <130 mg/dL; and patients with no or 1 risk factor(s) were assigned an LDL goal of <160 mg/dL. HDL goal was defined as ≥40 mg/dL for all patients.⁴ Patients were included in the model only if they had LDL levels above their calculated target goal. An HDL level less than 40 mg/dL was not used as a concomitant inclusion criterion.

The percent change in LDL and HDL at each dosing range of simvastatin or lovastatin/extended-release niacin was applied to the database to estimate the proportion of NHANES patients achieving LDL and HDL goal at each decision node (Table 1). Since no data were available in the product labeling for lovas-

ate laboratory tests conducted.¹⁶ This study was conducted from the perspective of a health care system. Table 2 summarizes the resource unit costs used in the analyses. Medicare's national average allowance fees were used to estimate 2002 costs associated with physician visits and laboratory tests.²⁷ Average wholesale prices (AWP) (Medispan, fall 2002) were used to estimate medication costs. The AWP values were averaged across package size and manufacturer/relabeler. The costs calculated from the model were the estimated total health care costs (medications, physician visit costs, and laboratory costs) to use each regimen for 4 months.

Sensitivity analysis testing was conducted to determine the impact of variable uncertainty on the models. Tornado diagrams were constructed for sensitivity analysis to determine which variables produced the greatest variation in end points. (A tornado diagram is useful to identify the range of model results

TABLE 2 Resource Unit Costs Used to Populate the Decision-Analytic Model

Resource Unit (Current Procedural Terminology Code)*	Cost (\$)
Physician visit 10 minute, minor problem (99212)*	36
Physician visit 25 minute, moderate/high severe (99214)*	79
Lipid panel (80061)*	58
Transaminase (84460 or 84450)*	19
Creatine kinase (82550)*	25
Simvastatin 20 mg (AWP)†	4.24
Simvastatin 40 mg (AWP)†	4.30
Simvastatin 80 mg (AWP)†	4.46
Lovastatin 20 mg/extended-release niacin 500 mg (AWP)†	1.45
Lovastatin 20 mg/extended-release niacin 750 mg (AWP)†	1.77
Lovastatin 20 mg/extended-release niacin 1,000 mg (AWP)†	1.89

* Costs determined using Physicians Fee and Coding Guide.²⁷

† Average wholesale price (AWP) determined using Medispan Fall 2002.

TABLE 3 Baseline Demographic Characteristics of the Treatment Groups

	Goal LDL <160 mg/dL + HDL ≥40 mg/dL N = 256	Goal LDL <130 mg/dL + HDL ≥40 mg/dL N = 1,268	Goal LDL <100 mg/dL + HDL ≥40 mg/dL N = 906
Age (mean, SD)	61.9 (14.8)	41.5 (15.1)	65.9 (13.7)
Male (%)	92 (35.9)	837 (66)	342 (37.7)
Total serum cholesterol mg/dL (mean, SD)	273.7 (33.9)	229.1 (28.5)	231.9 (39.0)
Serum triglycerides mg/dL (mean, SD)	146.4 (68.9)	130.6 (61.0)	167.3 (71.8)
Serum LDL cholesterol mg/dL (mean, SD)	188.7 (27.7)	156.2 (24.2)	154.4 (35.3)
Serum HDL cholesterol mg/dL (mean, SD)	55.7 (12.9)	46.7 (11.9)	44.0 (10.6)

LDL = low-density lipoprotein cholesterol.

HDL = high-density lipoprotein cholesterol.

obtained with a series of model variables.) Since statins have been shown to have a coefficient of variation of 17% in their LDL reduction, all clinical end point variables (lipid changes and adverse events) were modified by 25% higher and lower from the point estimates in the models.²⁸ Cost-sensitivity analyses were conducted by decreasing the medication costs by 25% for the most costly treatment strategy. In addition, sensitivity analyses were conducted to estimate cost changes over a 1-year study horizon. In the 1-year sensitivity analyses, it was assumed that there was 1 additional minor problem physician visit and 365 days of drug therapy based upon the dose for each pathway, 1 more lipid (laboratory) panel, and that previous treat-

ment remained discontinued if a patient encountered a significant adverse drug event.

Results

The analysis of the NHANES data based on LDL goal stratification revealed that, among dyslipidemic persons, there were 256 patients (10.5%) who required a goal of <160 mg/dL, 1,268 (52.2%) patients who required a goal of <130 mg/dL, and 906 patients (37.3%) who required a goal of <100 mg/dL. The baseline demographic characteristics of the patients are summarized in Table 3. Table 4 summarizes the success rate (i.e., proportion of patients achieving both LDL and HDL goals and not having a significant adverse event) and the cost for each regimen. It was noted that the proportion of patients achieving both LDL and HDL goals decreased with the more restrictive goal requirements for both regimens.

Figure 2 summarizes the cost-effectiveness ratios for both regimens at each treatment goal. These data demonstrate that lovastatin/extended-release niacin had lower (more favorable) cost-effectiveness ratios at each treatment LDL/HDL goal than did simvastatin.

Simvastatin had the highest clinical success rate in achieving both LDL and HDL goals in patients that required a LDL level <160 mg/dL and a HDL ≥40 mg/dL (97.2% versus 89.7% for lovastatin/extended-release niacin). However, the estimated total direct-medical cost (medications, physician visit costs, and laboratory costs) to use simvastatin was approximately twice that of lovastatin/extended-release niacin (\$665 versus \$333). Based on these estimates, the incremental cost-effectiveness ratio for each additional patient to reach LDL and HDL goals without an adverse event with simvastatin was \$4,427 when compared with lovastatin/extended-release niacin.

For both the 130 mg/dL and 100 mg/dL goal analyses, lovastatin/extended-release niacin had higher success rates than simvastatin (85.6% versus 76.7% and 63.7% versus 60.3%, respectively). In addition, for both the 130 mg/dL and 100 mg/dL goal analyses, lovastatin/extended-release niacin had lower estimated costs than simvastatin. Thus, in the incremental cost-effectiveness analyses for 130 mg/dL and 100 mg/dL LDL goal levels (plus HDL goal ≥40 mg/dL), lovastatin/extended-release niacin combination therapy dominated simvastatin monotherapy.

In the <160 mg/dL LDL and ≥40 mg/dL HDL goal model, sensitivity analysis demonstrated that 2 variables impacted the model success rates. Lowering the proportion of patients on simvastatin 20 mg who reach LDL and HDL goals from 0.891 to 0.730 and 0.991 to 0.741, respectively, lowered the overall simvastatin success rate to 0.897. Thus, lowering the simvastatin 20 mg lipid effects by 25% resulted in the same success rate as the baseline lovastatin/extended-release niacin. In another sensitivity analysis, when simvastatin medication costs were reduced by 25%, the estimated total direct-medical cost was reduced from \$665 to \$538. This yielded an incremental cost-

effectiveness ratio of \$2,733 for simvastatin for each additional patient to reach LDL and HDL goals without an adverse event compared with lovastatin/extended-release niacin.

For the <130 mg/dL LDL and $\geq$ 40 mg/dL HDL goal model, tornado diagram sensitivity analyses suggested that the clinical success rates were most sensitive to changes in HDL levels from either 20 mg of simvastatin or 20 mg/500 mg of lovastatin/extended-release niacin. When more than 86.8% of patients achieved HDL goal with simvastatin 20 mg, simvastatin was more successful than lovastatin/extended-release niacin. In the remaining sensitivity analyses, lovastatin/extended-release niacin was the most successful strategy throughout the range of other variables. When the simvastatin medication costs were reduced by 25%, the estimated total direct-medical cost was reduced from \$675 to \$548. Lovastatin/extended-release niacin continued to dominate simvastatin even when the simvastatin cost was lowered by 25% and was both more successful and less costly.

For the models with goals of <100 mg/dL LDL and $\geq$ 40 mg/dL HDL, tornado diagram sensitivity analyses suggested that the clinical success rates were most sensitive to the effect of simvastatin 20 mg on HDL, the LDL reduction with lovastatin/extended-release niacin 40 mg/1,000 mg, and the LDL lowering with lovastatin-extended-release niacin 40 mg/2,000 mg. When more than 76.6% of patients achieved HDL goal with simvastatin 20 mg, simvastatin was more successful than lovastatin/extended-release niacin. In sensitivity analyses with the other variables, lovastatin/extended-release niacin remained more successful throughout the variable ranges. When the simvastatin medication costs were reduced by 25%, the estimated total direct-medical cost was reduced from \$773 to \$645. Lovastatin/extended-release niacin continued to dominate simvastatin when the simvastatin cost was lowered by 25% and was both more successful and less costly.

One-year sensitivity analysis demonstrated an expansion in the estimated treatment cost differences between simvastatin and lovastatin/extended-release niacin. For the <160 mg/dL LDL and $\geq$ 40 mg/dL HDL goal model, the estimated cost of simvastatin was \$1,793 compared with \$792 for lovastatin/extended-release niacin. In the <130 mg/dL LDL and $\geq$ 40 mg/dL HDL goal model, the estimated cost of simvastatin was \$1,804 compared with \$929 for lovastatin/extended-release niacin. With the <100 mg/dL LDL and $\geq$ 40 mg/dL HDL goal model, the estimated cost of simvastatin was \$1,911 compared with \$1,354 for lovastatin/extended-release niacin. Figure 3 demonstrates the decision-tree variables with the greatest impact on treatment costs using the <100 mg/dL LDL and $\geq$ 40 mg/dL HDL goal model.

For drug costs, this study used AWP costs across package size and manufacturer/relabeler. A sensitivity analysis was also conducted by assuming flat pricing across all strengths of simvastatin and was assumed to be \$4.41 per tablet. Using the <100 mg/dL LDL and $\geq$ 40 mg/dL HDL goal model, the average cost of simvastatin increased from \$773 to \$789. Therefore, using flat dose

FIGURE 2 Cost to Achieve a Successfully Treated Patient

FIGURE 3 Tornado Diagram for LDL <100mg/dL and HDL $\geq$ 40 mg/dL

LDL = low-density lipoprotein cholesterol.
 HDL = high-density lipoprotein cholesterol.

pricing did not change the rank order of the alternatives.

Discussion

The ability to achieve goal cholesterol levels has enormous implications for patients, clinicians, and health care systems.^{1,3} This analysis demonstrated that, in the NHANES sample, most patients with dyslipidemia require LDL goals of less than either 130 mg/dL or 100 mg/dL. In targeting patient populations for LDL levels below 130 mg/dL or 100 mg/dL and HDL $\geq$ 40 mg/dL, lovastatin/extended-release niacin was both more successful and

TABLE 4 Clinical and Cost Outcomes for Simvastatin Monotherapy and Lovastatin/Niacin Combination Therapy for Each Designated Lipid Goal

Goal LDL + HDL ≥40 mg/dL	Simvastatin Success Rate (%)*	Simvastatin Cost (\$)	Lovastatin/ Extended-Release Niacin Success Rate (%)*	Lovastatin/ Extended-Release Niacin Cost (\$)	Incremental Cost-Effectiveness Ratio
<160 mg/dL	97.2	665	89	333	\$4,427 per additional successfully treated patient
<130 mg/dL	76.7	675	85.6	400	Lovastatin/ extended- release niacin dominates simvastatin
<100 mg/dL	60.3	773	63.7	616	Lovastatin/ extended- release niacin dominates simvastatin

*Success rate is defined as a patient achieving LDL and HDL goals and not experiencing a significant adverse event.

LDL = low-density lipoprotein cholesterol. HDL = high-density lipoprotein cholesterol.

less costly than simvastatin monotherapy.

The promotion of the ATP III treatment guidelines has importantly emphasized the role of LDL levels. In addition, this guideline has encouraged an examination of HDL levels, too. The VA-HIT and HATS studies suggest that patients may benefit from optimization of both LDL and HDL levels.^{6,7} Further research is needed to examine whether these long-term benefits are also observed with lovastatin/extended-release niacin.

The 3 decision-analytic models demonstrate that both treatment regimens had fewer patients achieve LDL and HDL goals as the goals became more restrictive. These results also indicate that the short-term direct-medical costs are larger, regardless of regimen, to achieve tighter lipid control. Long-term studies are needed to determine the clinical and economic outcomes with the goals being applied following publication of the ATP III guidelines.

These data are consistent with research from other investigators. Statins are highly regarded treatments and considered cost effective in the treatment of both secondary and primary prevention of dyslipidemia.²⁹⁻⁴⁰ Numerous evaluations have been conducted that support the important role of these products.⁴¹⁻⁴⁵ In addition, based on the VA-HIT trial, treatment with gemfibrozil to raise low HDL levels has been shown to be quite cost effective.⁴⁶ The complementary nature of extended-release niacin in combination with statin treatment has also been demonstrated.¹⁴⁻¹⁵ The data from this study support the rationale of using extended-release niacin in combination with statins. The formulation evaluated in this study (lovastatin/extended-release niacin) appears to be a cost-effective treatment alternative to simvastatin monotherapy in the majority of patients.

Although simvastatin had the highest success rate for the LDL <160 mg/dL and HDL ≥40 mg/dL goal levels, this regimen

had a total direct-medical cost almost twice that of lovastatin/extended-release niacin. The explanation for this observation appears to be the pricing of simvastatin that is the same regardless of dose for the 20 mg, 40 mg, and 80 mg doses (Table 2; the AWP for the 5 mg and 10 mg doses of simvastatin are lower than the 3 doses studied in this research). Although not often recommended, the practice of splitting the tablets of higher-dose simvastatin tablets would partially offset simvastatin's higher unit cost⁴⁷; splitting the 80 mg dose would reduce the 40 mg per day cost by 50%.

There are several important limitations that should be kept in mind when interpreting this study. Since no data were available in the product labeling for lovastatin/extended-release niacin 20 mg/500 mg formulation, the results from Kashyap²⁶ lovastatin/extended-release niacin 10 mg/500 mg were used as an estimate of cholesterol-level changes. Therefore, the model likely underestimated the number of patients reaching LDL and HDL goals at this dosage.

When incorporating medication costs, this study used AWP values. In a market economy with negotiated contract prices, actual purchase costs may be lower than AWP but would be similarly discounted across the products studied in this research. In addition, health systems may receive rebates from pharmaceutical manufacturers that would further lower the medication resource unit costs. Since contracts and rebates are confidential and variable by health system, this study relied upon AWP, a reasonable cost basis for this research since none of the products studied are available by generic name. In addition, the costs for statins may be expected to decrease in the future as additional products become available generically.⁴⁸

Another limitation with this study is the inability to account for variation in a patient's recommended lipid diet. Since diet can

independently impact cholesterol levels, this analysis was unable to incorporate this possible variability. A patient who is noncompliant with a recommended diet would be anticipated to have inferior lipid changes that are predicted with this model.

The basis of this study was that the NHANES III database was representative of the U.S. population. In addition, the effectiveness analysis in this study was based on the lipid changes in the product labeling for simvastatin and lovastatin/extended-release niacin. Lipid changes in actual practice may vary from those stated in the product labeling. Furthermore, this study used assumptions concerning the number of physician visits and laboratory tests needed to complete the titration schedules for both products. Actual practice patterns may vary between clinicians and health plans. The significant flushing rate with lovastatin/extended-release niacin was assumed to be a treatment failure in all cases and lowered the overall effectiveness for this product. In practice, it is possible that some patients may have tolerated the product with a slower titration schedule and/or administration of aspirin.

Conclusion

Both simvastatin and lovastatin/extended-release niacin are important agents to attain both LDL and HDL goals. This study demonstrated that simvastatin was more successful in achieving an LDL goal <160 mg/dL and an HDL goal $\geq$ 40 mg/dL. However, only a minority of patients requires this goal. The NHANES data demonstrate that the majority of U.S. residents require an LDL goal of <100 mg/dL or <130 mg/dL. For both of these goals—and the desired end point of HDL $\geq$ 40 mg/dL—lovastatin/extended-release niacin was both more successful and less costly than simvastatin.

DISCLOSURES

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