EFFICACY AND SAFETY OF CERIVASTATIN AND PRAVASTATIN IN THE TREATMENT OF PRIMARY HYPERCHOLESTEROLEMIA

Elijah Saunders, MD, Keith Ferdinand, MD, Laurence G. Yellen, MD, Melvin J. Tonkon, MD, Susan Krug-Gourley, BSN, MS, and Marcia Poland, MA

Baltimore, Maryland, New Orleans, Louisiana, San Diego, California, Anaheim, California, and Collegeville, Pennsylvania

In this randomized, double-blind, parallel group study, the efficacy and safety of cerivastatin (0.3 mg) and pravastatin (20 mg) were compared in 402 patients with primary hypercholesterolemia with and without documented coronary heart disease or peripheral vascular disease. After 8 weeks of treatment, cerivastatin provided significantly greater reductions than pravastatin in low-density lipoprotein (LDL)-cholesterol (31.1% vs. 26.0%; $p < 0.0001$) and total cholesterol (21.1% vs. 17.8%; $p < 0.0001$). A greater proportion of patients treated with cerivastatin than pravastatin achieved >30% and >40% reductions from baseline in LDL-cholesterol. Both agents also increased high density lipoprotein-cholesterol and reduced triglycerides. Overall, 65.1% of patients treated with cerivastatin and 63.3% of patients with pravastatin achieved LDL-cholesterol goals defined by the National Cholesterol Education Program. Both drugs were well tolerated, with most adverse events being mild. These results demonstrate that cerivastatin (0.3 mg) is a highly effective 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitor, which enables a large proportion of patients to achieve clinically meaningful reductions in LDL-cholesterol. (*J Natl Med Assoc.* 2000;92:319–326.)

Key words: hypercholesterolemia ♦ cardiovascular disease ♦ cerivastatin ♦ pravastatin

Long-term epidemiological studies provide convincing evidence that hypercholesterolemia increases risk for acute myocardial infarction and death from coronary heart disease (CHD).[1,2] Correspondingly, clinical trials demonstrate that lowering serum lipids, especially low density lipoprotein (LDL)-cholesterol, reduces cardiovascular outcomes in hypercholesterolemic patients with or without established CHD.[3–6] Moreover, LDL-cholesterol lowering may slow progression and even permit regression of atherosclerotic lesions.[7,8] The introduction of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors ("statins") represented a major advance in the management of hypercholesterolemic patients, because these drugs combine high efficacy for lowering LDL-cholesterol with an attractive safety and tolerability profile. Statins inhibit the key enzyme involved in hepatic cholesterol synthesis. Differences in LDL-cholester-

 From the Department of Hypertension, University of Maryland Medical Center, Baltimore, MD; the Heartbeats Life Center, New Orleans, LA; the Cardiology Associates Medical Group of E. San Diego, Inc., San Diego, CA; the Anaheim Heart and Research Institute, Anaheim, CA; and the Cardiovascular Therapeutic Unit, SmithKline Beecham Pharmaceuticals, Collegeville, PA. Requests for reprints should be addressed to Elijah Saunders, MD, Department of Hypertension, University of Maryland Medical Center, 419 W. Redwood St., Suite 620, Baltimore, MD 21201.

ol-lowering efficacy among members of this drug class have been reported.[9]

Cerivastatin is a fully synthetic, pure enantiomeric pyridine derivative that has very high affinity for the HMG-CoA reductase enzyme.[10] In patients with primary hypercholesterolemia, cerivastatin lowers LDL-cholesterol in a dose-dependent manner, with a once daily dose of 0.3 mg providing 31% reduction.[11,12] Moreover, cerivastatin further enhances the lipid profile by increasing HDL-cholesterol and reducing triglycerides, especially among patients with elevated baseline triglyceride levels.[12–14]

Valid comparisons of the lipid-lowering properties of two statins can only be made by a "head to head" comparison of the statins within the same study. In several published studies, pravastatin, 20 mg once daily, at bedtime reduced LDL-cholesterol by 25%–32%. Changes in high density lipoprotein (HDL)-cholesterol in these studies were variable.[15–18] Therefore, the primary objective of this study was to compare cerivastatin (0.3 mg) and pravastatin (20 mg) in terms of LDL-cholesterol lowering, and as a secondary objective, to compare the effects of these agents on total cholesterol, HDL-cholesterol, triglycerides, and the ratios of LDL-cholesterol to HDL-cholesterol and total cholesterol to HDL-cholesterol.

METHODS

Patients

Male or female patients aged 18 to 75 years with a diagnosis of type IIa or IIb hypercholesterolemia were eligible if they had been on the American Heart Association Step I or Step II diet for at least 2 weeks and had triglyceride levels <400 mg/dL. All patients provided written informed consent. Subjects with a history of myocardial infarction (within the previous year), unstable angina, angina at rest, stroke or recent transient ischemic attacks, recent coronary revascularization, uncontrolled hypertension or hypothyroidism, diabetes, chronic liver disease, renal dysfunction, or drug or alcohol abuse were excluded. Patients with confirmed creatine phosphokinase levels >3 times the upper limit of normal (ULN) were also excluded. Concomitant treatment with oral corticosteroids, macrolide antibiotics, androgens, anticoagulants, immunosuppressants, hypolipidemic agents, or antifungal agents was not permitted.

Study Design

This randomized, parallel group study was conducted at 28 centers in the United States (see Appendix 1 for investigator sites) and included two phases—a 6- to 8-week run-in phase and an 8-week double-blind treatment phase. Patients remained on their Step I or II diets throughout the study. At screening, patients provided a medical history and written informed consent and then discontinued any previous lipid-lowering therapy. Patients returned to the study center 2 or 4 weeks later, depending on whether they had received previous lipid-lowering treatment. Additional visits were scheduled 2, 3, and 4 weeks thereafter. Fasting lipid profiles were determined, the Step I diet (or Step II for 9 patients) was reviewed, and medication usage and adverse events were recorded at each office visit during the run-in phase. Patients with reproducible LDL-cholesterol levels (i.e., did not vary by more than 20%) above their National Cholesterol Education Program (NCEP)-recommended goal (i.e., >160 mg/dL for patients with 0 to 1 risk factor, >130 mg/dL for those with >2 risk factors, or >100 mg/dL for those with documented CHD or peripheral vascular disease [PVD]) were randomized to treatment with cerivastatin (0.3 mg) or pravastatin (20 mg) once daily at bedtime. Fasting lipid profiles, concomitant medication usage, and adverse events were recorded every 2 weeks during double-blind treatment.

Assessments

Total cholesterol and triglycerides were determined after patients had fasted for at least 12 hours. HDL-cholesterol was determined using the heparin-manganese chloride precipitation method, and LDL-cholesterol was calculated by the Friedewald equation (LDL-cholesterol = total cholesterol − HDL-cholesterol − 1/5 triglycerides). The ratios of total cholesterol to HDL-cholesterol and LDL-cholesterol to HDL-cholesterol were calculated. Returned capsules at each study visit were used to evaluate adherence to study medication, and a food intake diary was reviewed at two visits in the run-in phase and at the final two visits of the double-blind phase to determine adherence with the Step I diet. Safety was assessed from adverse events, laboratory tests, and physical examinations. All volunteered or observed adverse events were recorded at each visit, and an assessment of their seriousness, intensity,

Table 1. Patient Demographics

Characteristic	Cerivastatin (0.3 mg) (n = 221)	Pravastatin (20 mg) (n = 223)
Age (y): mean ± SE	58.4 ± 0.8	58.2 ± 0.7
Weight (lbs): mean ± SE	182.9 ± 2.4	183.4 ± 2.3
Gender		
Male	115 (52.0%)	128 (57.4%)
Female	106 (48.0%)	95 (42.6%)
Race		
White	192 (86.9%)	199 (89.2%)
African American	17 (7.7%)	14 (6.4%)
Asian	7 (3.2%)	1 (0.4%)
Other	5 (2.2%)	9 (4.0%)

and relationship to study medication was made by the investigator. Laboratory tests, which included measurements of creatine phosphokinase, liver enzymes, serum creatine, fasting blood sugar, and blood urea nitrogen, were done twice during the run-in phase and after 4 and 8 weeks of treatment with cerivastatin and pravastatin. An ECG and a physical examination, which included assessment of seated vital signs and body weight, were conducted during the run-in phase and at the final visit of the double-blind phase.

Data Analysis

The primary efficacy endpoint was percentage of decrease from baseline in LDL-cholesterol, which was calculated from the mean from the final three measurements of the run-in period and the mean of the final two measurements of the double-blind period. Secondary endpoints included the percentage of patients meeting their NCEP goal for LDL-cholesterol; the percentage change and absolute change in total cholesterol, HDL-cholesterol, and triglycerides; and the change in the ratios of total or LDL-cholesterol to HDL-cholesterol. An analysis of variance (ANOVA) model with terms for treatment, investigator, and treatment by investigator interaction was used to evaluate mean percentage changes and mean changes from baseline in lipid parameters. Differences between treatments were estimated using least-square means, with 95% confidence intervals (CI) constructed by using normal approximation and an estimate of variation from the least-squares means option of the general linear models procedure of SAS. The proportion of patients achieving their NCEP LDL-cholesterol goals (<160 mg/dL for patients with 0 to 1 risk factor, and <130 mg/dL for patients with >2 risk factors but without CHD or PVD, and <100 mg/dL for those with documented CHD or PVD)[19] was evaluated via logistic analysis using categorical modeling. A p-value of <0.05 was indicative of statistical significance between treatments. All patients who met the protocol requirements were included in the efficacy analysis, whereas all patients who received a dose of double-blind medication were included in the safety analysis.

RESULTS

During the double-blind treatment period, 221 patients received cerivastatin (0.3 mg) and 223 patients received pravastatin (20 mg). The two treatment groups were well matched with respect to patient demographics. The average patient age was 58 years, with a large majority of patients being white (88%) and a slight majority being male (55%) (Table 1). Of these patients, 19 in the cerivastatin group and 23 in the pravastatin group did not satisfy protocol-defined LDL requirements (all but two patients had LDL values that did not meet the entrance criteria, and the other two had prohibited concomitant diseases) and were excluded from the efficacy analysis. As shown in Table 2, patients in the cerivastatin and pravastatin groups were comparable with respect to baseline lipid levels and distribution among the three NCEP risk groups. The majority of patients were compliant (80%–120%) with the Step I/II diet (60% of patients in the cerivastatin group and 59% of patients in the pravastatin group). Compliance with study drug was higher (96% in both treatment groups).

Cerivastatin (0.3 mg) reduced LDL-cholesterol by 31.1% from baseline, which was significantly bet-

Table 2. Clinical Characteristics of Patients Valid for the Efficacy Analysis

	Cerivastatin (0.3 mg) (*n* = 202)	Pravastatin (20 mg) (*n* = 200)
Baseline lipids (mg/dL): mean ± SE		
Total cholesterol	264.6 ± 2.2	258.2 ± 2.5
LDL-cholesterol	179.0 ± 2.0	172.3 ± 2.1
HDL-cholesterol	50.9 ± 0.9	50.9 ± 0.9
Triglycerides	173.9 ± 4.5	175.3 ± 4.5
NCEP risk group:		
0 to 1 risk factor without CHD/PVD	69 (34%)	66 (33%)
≥2 risk factors without CHD/PVD	88 (44%)	85 (43%)
Documented CHD or PVD	45 (22%)	49 (24%)

ter than the 26.0% reduction with pravastatin (20 mg) ($p < 0.0001$) (Figure 1). The least-square mean difference between treatments (and 95% CI) was 5.1% (−7.1% to −3.1%) in favor of cerivastatin (0.3 mg). LDL-cholesterol was reduced by a mean of 55.7 mg/dL from a baseline level of 179.0 mg/dL with cerivastatin, whereas it was reduced by a mean of 44.8 mg/dL from a baseline level of 172.3 mg/dL with pravastatin. Overall, a higher percentage of patients treated with cerivastatin had greater percentage reductions in LDL-cholesterol. As shown in Figure 2, 56% and 18% of patients in the cerivastatin group had >30% and >40% reductions in LDL-cholesterol, whereas only 36% and 6%, respectively, of patients in the pravastatin group achieved these responses.

Cerivastatin (0.3 mg) and pravastatin (20 mg) reduced total cholesterol, increased HDL-cholesterol, and lowered triglycerides (Figure 1). The reduction in total cholesterol was significantly greater with cerivastatin than with pravastatin (21.1% vs. 17.8%; $p < 0.0001$), whereas the changes in HDL-cholesterol and triglycerides did not differ significantly between treatments. The effect of treatment on triglycerides was dependent on baseline triglyceride levels (Figure 3). In the subgroup of patients with baseline triglycerides <200 mg/dL, cerivastatin and pravastatin reduced triglycerides by 6.7% and 6.6%, respectively. However, in patients with higher baseline triglycerides (≥200 mg/dL), both drugs provided greater reductions in triglycerides, 13.1% and 15.1%, respectively. Overall, cerivastatin was better than pravastatin in improving the lipid profile as reflected by decreases from baseline in the ratios of LDL-cholesterol:HDL-cholesterol (−35.0% vs. −28.8%; $p < 0.0001$) and total cho-

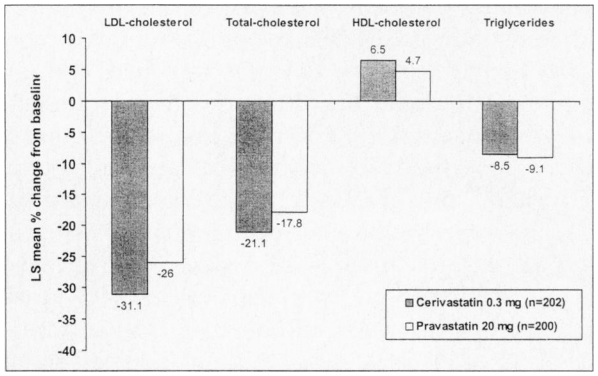

Figure 1. Change in lipid levels with cerivastatin or pravastatin treatment. Plotted is the least-squares mean percent change from baseline in LDL-cholesterol, total cholesterol, HDL-cholesterol, and triglycerides.

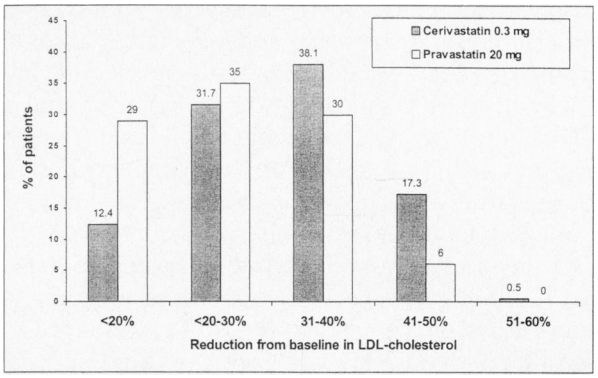

Figure 2. Distribution of LDL-cholesterol reduction after treatment with cerivastatin or pravastatin. Plotted is the percentage of patients with reductions from baseline in LDL-cholesterol of <20%, 21%–30%, 31%–40%, 41%–50%, and 51%–60%.

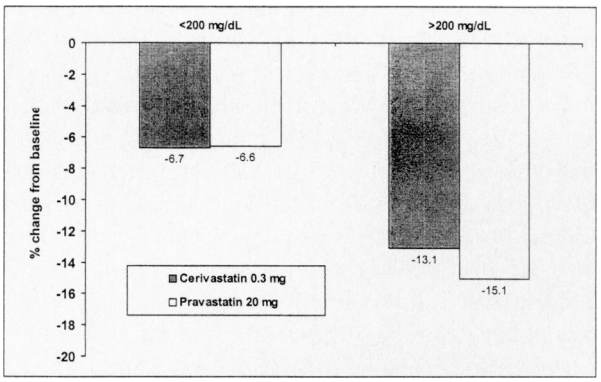

Figure 3. Change in triglycerides with cerivastatin or pravastatin treatment according to baseline triglyceride levels. Patients were stratified according to whether they had lower (<200 mg/dL) or higher (≥200 mg/dL) triglycerides at baseline.

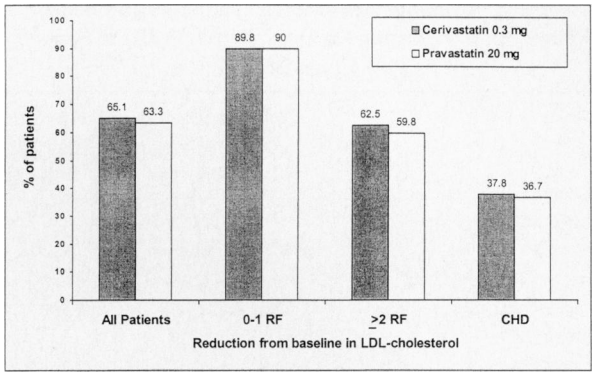

Figure 4. Percentage of patients achieving NCEP-defined goals. As specified in NCEP guidelines, the LDL-cholesterol goals were <160 mg/dL and <130 mg/dL for those with 0 to 1 and ≥2 risk factors without CHD or PVD and >100 mg/dL for those with documented CHD or PVD.

lesterol:HDL-cholesterol (−25.6% vs. −21.0%; $p < 0.0001$).

A significant percentage of patients achieved their NCEP-defined LDL-cholesterol goals with both statins. Overall, 65.1% of patients achieved NCEP goals with cerivastatin (0.3 mg) as did 63.3% of patients with pravastatin (20 mg) (Figure 4). The vast majority (89.8%–90%) of patients with 0 to 1 risk factor without CHD or PVD achieved their LDL-cholesterol goal of <160 mg/dL. In the other two risk groups, the percentage of patients achieving NCEP goals was numerically higher with cerivastatin. Among patients with ≥2 risk factors without CHD or PVD, 62.5% and 59.8% achieved NCEP goals with cerivastatin and pravastatin treatment, respectively, whereas, among those with documented CHD or PVD, 37.8% and 36.7% were successful with cerivastatin and pravastatin, respectively.

Cerivastatin and pravastatin were well tolerated, with the majority of adverse events rated as mild in intensity. The mean and median durations of treatment were the same in both groups, being 54 and 56 days, respectively. Overall, at least one adverse event occurred in 91 (41.2%) patients in the cerivastatin group and 83 (37.2%) patients in the pravastatin group. In terms of individual adverse events, noticeable differences between treatments were not evident (Table 3). Eight (3.6%) patients in the cerivastatin group and 4 (1.8%) patients in the pravastatin group withdrew due to adverse events; only one event in the cerivastatin group (moderate myalgia) and two (moderate headache, mild abdominal pain) in the pravastatin group were considered by the investigator likely to be related to study treatment. Liver enzymes were not elevated to greater than three times the ULN in any patient. Elevations in creatine phosphokinase to greater than three times ULN were observed in four patients in the cerivastatin group and one in the pravastatin group. There were no significant changes in mean vital signs or ECG changes related to study treatment.

DISCUSSION

The results of this study demonstrate that cerivastatin (0.3 mg) provides significantly greater LDL-cholesterol lowering than pravastatin (20 mg). After 8 weeks of treatment, cerivastatin lowered LDL-cholesterol by 31.1%, whereas pravastatin lowered it by 26.0% ($p < 0.0001$). As a result, a higher percentage of patients treated with cerivastatin than pravastatin achieved reductions in LDL-cholesterol that were >30% and >40% from baseline. Moreover, cerivastatin enabled a numerically higher percentage of patients in the two highest cardiovascular risk groups to achieve their NCEP-defined goals for LDL-cholesterol. Both statins also reduced total cholesterol and increased HDL-cholesterol. The reduction in total cholesterol was significantly greater with cerivastatin than with pravastatin ($p < 0.0001$). The increase in HDL-cholesterol, although numerically greater with cerivastatin, did not differ significantly between treatments ($p = 0.068$). Overall, cerivastatin provided significantly greater percent-

Table 3. Incidence of Adverse Events (Regardless of Relationship to Treatment Occurring in ≥3% of Patients in Either Group)

Adverse Event	Cerivastatin (0.3 mg) (*n* = 221)	Pravastatin (20 mg) (*n* = 223)
Headache	9 (4.1%)	8 (3.6%)
Sinusitis	7 (3.2%)	9 (4.0%)
Injury	7 (3.2%)	8 (3.6%)
Upper respiratory tract infection	6 (2.7%)	8 (3.6%)
Diarrhea	2 (0.9%)	7 (3.1%)

Data expressed as number (%) of patients.

age reductions in the ratios of LDL-cholesterol: HDL-cholesterol and total cholesterol:HDL-cholesterol than did pravastatin (both $p < 0.0001$).

The reductions in LDL-cholesterol with cerivastatin (0.3 mg) and pravastatin (20 mg) are similar to those reported previously. In an 8-week, placebo-controlled, double-blind study, cerivastatin (0.3 mg) reduced LDL-cholesterol by 33% among 140 patients with primary hypercholesterolemia, and furthermore, 29% of these patients had >40% reductions in LDL-cholesterol.[11] When the results of several 8-week studies exclusive of this study were combined, cerivastatin (0.3 mg) lowered LDL-cholesterol by 31.3% among 408 patients with primary hypercholesterolemia.[12] Several studies have evaluated pravastatin (20 mg) once daily at bedtime and found reductions in LDL-cholesterol ranging from 25% to 32%.[15–18] In the largest study, which involved 1062 patients with primary hypercholesterolemia, >2 risk factors but no CHD, and baseline total cholesterol of 200 to 300 mg/dL, pravastatin (20 mg) reduced LDL-cholesterol and total cholesterol by 26% and 19%, respectively and increased HDL-cholesterol by 7%.[16] These findings are almost identical to those in the present study, which involved patients with primary hypercholesterolemia in all three NCEP risk groups.

Studies in patients with and without documented CHD demonstrate that LDL-cholesterol lowering with statins significantly reduces cardiovascular outcomes.[4–6,20] Several long-term studies have evaluated the effect of pravastatin on clinical outcomes; however, these have been conducted with the 40-mg dose. The Cholesterol and Recurrent Events (CARE) study[6] and the Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) study[20] demonstrate that pravastatin (40 mg) reduced cardiovascular morbidity and mortality in CHD patients, whereas the West of Scotland Coronary Prevention Study (WOSCOPS)[5] showed that primary prevention with pravastatin (40 mg) reduced risk for coronary events and CHD mortality. The effect of cerivastatin on cardiovascular morbidity and mortality has not yet been determined. In addition, it remains to be determined whether the higher efficacy of cerivastatin will translate into improved clinical outcomes relative to that of pravastatin.

In addition to lowering LDL-cholesterol and improving the overall lipid profile, cerivastatin and pravastatin were safe and well tolerated, with most adverse events being mild in intensity. These results demonstrate that cerivastatin (0.3 mg) is a highly effective HMG-CoA reductase inhibitor, which enables a larger proportion of patients to achieve clinically meaningful reductions in LDL-cholesterol than does pravastatin.

APPENDIX 1

Principal Investigators in this study include: Paul S. Abdallah, MD (Minor and James Clinical Research, PLLC, Seattle, WA); Thomas C. Andrews, MD (University of Texas, Southwestern Medical Center at Dallas, Dallas, TX); Roger S. Blumenthal, MD (The Johns Hopkins University, Division of Cardiology, Baltimore, MD); Bruce K. Bowen, MD (Camino Medical Group, Sunnyvale Clinic, Sunnyvale, CA); John A. Bowers, MD (Heart Institute of Nevada, Las Vegas, NV); Carlos de la Garza, MD (Unifour Medical Research Associates, Hickory, NC); James V. Felicetta, MD and Carl T. Hayden, MD (Veteran's Affairs Medical Center, Phoenix, AZ); Keith C. Ferdinand, MD (Heartbeats Life Center, New Orleans, LA); Marvin Galler, MD (Amherst Cardiology & Internal Medicine Associates, Williamsville, NY); Russell K. Havlicek, MD (Wenatchee Valley Clinic, Wenatchee, WA); Nicholas Z. Kerin, MD (Sinai Hospital, Detroit, MI); Athol W. Morgan, MD (Urban Medical Institute, Baltimore, MD); William S. Mullican, MD (Medisphere Medical Research Center, Evansville, IN); William E. Neighbor, MD (Department of Family Medicine, Seattle, WA); Joel M. Neutel, MD (Orange County Research Center, Orange, CA); Alan L. Niederman (The Greater Fort Lauderdale Heart Institute Research Group, Ft. Lauderdale, FL); Robert Z. Paster, MD (Dean Med-

ical Center, Oregon, WI); Frank S. Pettyjohn, MD (University of South Alabama College of Medicine, Mobile, AL); Dennis A. Ruff, MD (South Texas Clinical Trials PA, San Antonio, TX); Gordon M. Saperia, MD (Fallon Clinic, Worcester, MA); Elijah Saunders, MD (University of Maryland Department of Medicine, Division of Hypertension, Baltimore, MD); James J. Stamper, MD (The Sutherland Clinic, Inc., Memphis, TN); Melvin J. Tonkon, MD (Anaheim Heart and Research Institute, Anaheim, CA); Robert C. Touchon, MD (Marshall University School of Medicine, Huntington, WV); Brad J. Wallum, MD (Eastside Endocrinology & Diabetes, Bellevue, WA); Martin S. Weiss, MD (University of North Texas Health Science Center, Fort Worth, TX); Francine K. Welty, MD (Beth Israel Deaconess Medical Center, Boston, MA); Duane G. Wombolt, MD (Clinical Research Associates of Tidewater, Norfolk, VA); Laurence G. Yellen, MD (Cardiology Associates Medical Group of East San Diego, Inc., San Diego, CA); and Randall M. Zusman, MD (Massachusetts General Hospital, Boston, MA).

APPENDIX 2
CME Objectives and Questions*

Learning Objectives.

1. To define the lipid-lowering profile of cerivastatin (0.3 mg) in patients with primary hypercholesterolemia.
2. To compare the LDL-cholesterol-lowering efficacy of cerivastatin (0.3 mg) and pravastatin (20 mg) in patients with primary hypercholesterolemia.
3. To compare the effects of cerivastatin (0.3 mg) and pravastatin (20 mg) on total cholesterol, HDL-cholesterol, and triglycerides.

CME Questions.

1. What does treatment with cerivastatin (0.3 mg) achieve in patients with primary hypercholesterolemia?

a. A mean reduction in LDL-cholesterol of approximately 15%.
b. A mean reduction in LDL-cholesterol of approximately 23%.
c. A mean reduction in LDL-cholesterol of approximately 30%.
d. A mean reduction in LDL-cholesterol of approximately 38%.

2. In patients with primary hypercholesterolemia,

a. cerivastatin (0.3 mg) and pravastatin (20 mg) lower LDL-cholesterol and total cholesterol to the same extent.
b. cerivastatin (0.3 mg) provides significantly greater reductions in LDL-cholesterol and total cholesterol than pravastatin (20 mg).
c. pravastatin (20 mg) provides significantly greater reductions in LDL-cholesterol and total cholesterol than cerivastatin (0.3 mg).
d. few patients achieve NCEP-defined LDL-cholesterol goals with either cerivastatin (0.3 mg) or prayastatin (20 mg).

3. Which of the following statements is correct?

a. In patients with primary hypercholesterolemia, cerivastatin (0.3 mg) provides significantly greater effects on total cholesterol, HDL-cholesterol, and triglycerides than pravastatin (20 mg).
b. In patients with primary hypercholesterolemia, cerivastatin (0.3 mg) and pravastatin (20 mg) have comparable effects on serum lipid profiles.
c. In patients with primary hypercholesterolemia, cerivastatin (0.3 mg) provides significantly greater reductions in total cholesterol than pravastatin (20 mg), but the effects on HDL-cholesterol and triglycerides do not differ significantly.
d. In patients with primary hypercholesterolemia, cerivastatin (0.3 mg) and pravastatin (20 mg) are not expected to lower triglycerides unless baseline levels are elevated.

*The answers are: 1 (c); 2 (b); 3 (c).

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