Ciprofibrate Versus Gemfibrozil in the Treatment of Mixed Hyperlipidemias: An Open-Label, Multicenter Study

Carlos Alberto Aguilar-Salinas, Guillermo Fanghänel-Salmón, Edilberto Meza, Juan Montes, Alfonso Gulías-Herrero, Leticia Sánchez, Eric A. Monterrubio-Flores, Héctor González-Valdez, and Francisco J. Gómez Pérez

Mixed hyperlipidemia is a common risk factor for cardiovascular disease. The aim of this trial was to evaluate the efficacy and safety of ciprofibrate versus gemfibrozil for the treatment of patients with mixed hyperlipidemia carefully selected for similar lipid profiles. A total of 68 patients who had mixed hyperlipidemia after following an isocaloric American Heart Association (AHA) phase I diet for 4 weeks were included. The plasma lipid levels at the inclusion were low-density lipoprotein-cholesterol (LDL-C) ≥ 130 mg/dL, cholesterol ≥ 240 mg/dL, and triglycerides ≥ 200 mg/dL. Patients were randomly assigned to receive ciprofibrate 100 mg/d or gemfibrozil 1,200 mg/d. At the end of the 8-week treatment period, efficacy and safety parameters were compared with baseline values. The primary efficacy parameters of the study were percentage changes in triglycerides and LDL-C from baseline. After 8 weeks, plasma triglyceride concentrations were decreased by 43.5% and 54% compared with baseline during ciprofibrate and gemfibrozil therapy, respectively ($P < .001$). High-density lipoprotein-cholesterol (HDL-C) concentrations were increased 20.8% and 19.3% during ciprofibrate and gemfibrozil, respectively ($P < .001$). Apoprotein B, cholesterol, and very–low-density lipoprotein-cholesterol (VLDL-C) concentrations were also improved by the study drugs (18.6%, 13.2%, and 30.9%, respectively, during ciprofibrate and 44%, 13.8%, and 14.4%, respectively, during gemfibrozil). Meanwhile, the effect of the drug was minimal on LDL-C. A significant decrease in non–HDL-C resulted from both treatments (19% and 19.5%, respectively, $P < .05$). The only statistically significant difference observed between treatments was the effects on fibrinogen concentration, a coronary risk factor. Ciprofibrate significantly decreased its concentration by 18.8%, fibrinogen was slightly increased during gemfibrozil treatment. No patient had a significant modification on any of the safety tests. In summary, ciprofibrate and gemfibrozil are well-tolerated and efficacious treatments for mixed hyperlipidemia. Significant reductions in triglycerides, non–HDL-C, and apolipoprotein B were achieved with both drugs. A significant fibrinogen reduction was obtained with ciprofibrate.

Copyright © 2001 by W.B. Saunders Company

MIXED HYPERLIPIDEMIA, characterized by the presence of elevated plasma concentrations of cholesterol and triglycerides, is 1 of the most common and atherogenic abnormalities of lipid metabolism.[1] Derived from a combination of overproduction of triglyceride-rich particles[2,3] and catabolic defects of the apoprotein B containing particles, mixed hyperlipidemia can be either primary in origin or a secondary manifestation of several diseases. In the Prospective Cardiovascular Münster Study (PROCAM),[4] the 6-year incidence of coronary events was 13.7 times higher compared with the control subjects. The attributable risk for mixed hyperlipidemias was among the highest, preceded only by the observed cases with the most severe hyperlipidemias (cholesterol > 300 mg/dL and/or triglycerides > 500 mg/dL). The risk was even higher when low high-density lipoprotein-cholesterol (HDL-C) (< 35 mg/dL) concentrations coexisted. The prevalence of hypertriglyceridemia in Mexican adults 20- to 69-years old is 22.4%.[5] The vast majority of them (88%) have concentrations between 200 to 500 mg/dL, levels usually observed in mixed hyperlipidemia subjects.

The goal of the treatment of mixed hyperlipidemia is to normalize the lipid profile and, by that means, prevent death and morbidity from vascular disease.[6] Dietary therapy together with modifications in lifestyle, such as weight reduction and increased physical activity, may have an impact in reducing abnormal lipid levels, but usually 1 or 2 lipid-lowering drugs are required.[7] The drugs usually indicated are fibrates and/or statins.[8] The interest for using fibrates in primary and secondary prevention have grow enormously in the past few years due to the discovery of its molecular mechanism of action[9] and the results of the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VAHIT) and Bezafibrate Coronary Atherosclerosis Intervention Trial (BECAIT) studies.[10,11] The VAHIT study[10] showed that in patients whose primary lipid abnormality is a low HDL-C, increasing HDL cholesterol 6% and lowering triglycerides 31% in the absence of a reduction of low-density lipoprotein-cholesterol (LDL-C) levels results in a clinical benefit comparable to that obtained in the statins trials in patients with moderate hypercholesterolemia. However, there is a lack of this type of data in patients with mixed hyperlipidemia.

Ciprofibrate and gemfibrozil are among the most commonly prescribed fibrates. Both drugs are effective in the treatment of hypertriglyceridemia and mixed hyperlipidemia. However, a direct comparison of the effects of these drugs in mixed hyperlipidemia has not been reported. Differences have been observed in the biologic actions of the fibrates.[12] Significant variability in responses has been observed; the LDL-C concen-

From the Departamento de Endocrinología y Metabolismo, Instituto Nacional de la Nutrición; Departamento de Endocrinología, Hospital General de México, México City, Mexico; Departamento de Medicina Interna, Pensiones Civiles del Estado de Chihuahua, Ciudad Juarez, Chihuahua, Mexico; Hospital Universitario, Universidad Autónoma de Nuevo León, Nuevo León, Mexico; and the Instituto Nacional de Cancerología, México City, Mexico.

Submitted October 2, 2000; accepted December 18, 2000.

Supported by an unrestricted grant from SANOFI-Synthelabo.

Address reprint requests to Carlos A. Aguilar-Salinas, MD, Departamento de Endocrinología y Metabolismo, Instituto Nacional de la Nutrición, Vasco de Quiroga 15, Mexico City 14000, Mexico.

Copyright © 2001 by W.B. Saunders Company

0026-0495/01/5006-0017$35.00/0

doi:10.1053/meta.2001.23308

tration has been decreased from 5% to 30%[12-15] using any of these drugs. Some of this variability may be explained by the heterogeneity of the dyslipidemia of the subjects included in most parts of the studies. In 1 of the few published studies in which a direct comparison of ciprofibrate and gemfibrozil was performed, at baseline, patients with a primary hyperlipidemia[16] had a wide range in cholesterol (323 to 391 mg/dL) and triglyceride (178 to 338 mg/dL) concentrations. The inclusion of different lipid profiles (hypercholesterolemia with or without hypertriglyceridemia) resulted in a wide range of lipid responses. It is clear that drugs must be compared in patients having the same type and severity of lipid abnormality. Additional research is needed to assess the efficacy and safety of fibrates and/or statins in well-defined group of dyslipidemias, ie, primary mixed hyperlipidemias. The objectives of this study were to assess the efficacy and safety of 100 mg/d ciprofibrate for the treatment of mixed hyperlipidemia. The therapeutic action was compared with gemfibrozil (1,200 mg/d), because it is the most extensively investigated and most commonly used fibrate.

MATERIALS AND METHODS

Patients

The trial included men and postmenopausal or nonpregnant women between the ages 18 and 65 years who had a mixed hyperlipidemia even after following an isocaloric American Heart Association (AHA) phase I diet for 4 weeks.[17] The plasma lipid levels required at inclusion were LDL-C $\geq$ 130 mg/dL, cholesterol $\geq$ 240 mg/dL, and triglycerides $\geq$ 200 mg/dL. Patients were excluded if they had type 1 diabetes, uncontrolled hypertension, severe renal dysfunction, nephrotic syndrome or dysproteinemias, fasting plasma triglycerides greater than 900 mg/dL, aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels greater than 1.5 the upper limit of normal (ULN), or if their creatine phosphokinase (CPK) levels were greater than 3 ULN. Consumption of any lipid-altering drug within the previous 4 weeks (6 months for probucol) prevented entry into the study. Patients could be receiving other concomitant medications as long as the dosage was not modified during the study.

The Ethics Committee of each of the institutions approved the protocol, and every patient provided witnessed, written informed consent before entering the study.

Study Design

This was a multicenter, open-label, 8-week study. Patients attended an initial screening visit followed by a qualifying visit 4 weeks later in which a physical examination, body weight, and compliance with diet were assessed and blood samples taken. Patients who fulfilled the inclusion criteria were included and drug treatment was started. Throughout the trial, including the pretreatment period of 4 weeks, patients were required to comply with an isocaloric, standard lipid-lowering diet defined by a registered dietician of 50% carbohydrates, 20% protein, 30% fat, and 30 g/d fiber. Dietary advice was given at the initial visit and compliance with the diet assessed at every subsequent visit (at 4-week intervals) using a 3-day food record. Drug compliance, body weight, and safety, as well as laboratory parameters, were measured at every visit.

Treatments

Patients were randomly assigned to receive ciprofibrate 100 mg at bedtime or gemfibrozil 600 mg twice a day using a previously prepared database. In order to keep the attending physicians blinded to the treatment, the accountability of drug was made by other members of the study group.

Efficacy Parameters

At the end of the 8-week treatment period, efficacy was assessed by comparison with baseline values. In all cases, baseline values were obtained during the second visit (after 4 weeks of diet). The primary efficacy parameters of the study were percentage changes in triglycerides and LDL-C from baseline. Secondary efficacy parameters included the percentage changes in total cholesterol, HDL-C, non–HDL-C, and apolipoprotein B from baseline. Non–HDL-C is obtained by substracting the HDL-C from the total cholesterol levels.

Safety Evaluation

Before entering the study, patients underwent a complete physical examination with clinical laboratory evaluation, including blood count, measurement of thyroid-stimulating hormone (TSH) and CPK levels, urinalysis, ALT and AST levels, fasting plasma glucose, and a pregnancy test. These tests were repeated at the end of the study. At each visit, AST, ALT, fasting plasma glucose, and CPK levels were measured. Potentially clinically relevant events were defined as CPK $> 5 \times$ ULN at 2 consecutive measurements 1 week apart accompanied by muscle pain, tenderness, or weakness; CPK $> 10 \times$ ULN at any time; ALT or AST $> 3 \times$ ULN at 2 consecutive measurements 1 week apart. Patients were excluded from the study if they developed severe hyperglycemia or any other significant deviation from safety tests. Other reasons for premature withdrawal were lack of compliance to the drugs or diet.

Laboratory Analyses

All samples were analyzed in a central laboratory (ESRD Specialty Laboratories, Fort Lauderdale, FL). Blood samples were taken after an overnight fast ($\geq$ 9 hours). All laboratory analyses were performed with commercially available standardized methods. Glucose was measured using the glucose oxidase method. Total serum cholesterol and triglyceride levels were measured using an enzymatic method (SERA-PAK, Bayer, Tarrytown, NY) (coefficient of variation [CV], 3.3%). HDL-C levels were assessed using phosphotungstic acid and Mg^{2+} (CV, 2.5). Direct LDL-C was determined by ultracentrifugation (β quantification) at week 0, on completion of 16 weeks of treatment, and in every patient in whom triglyceride levels were greater than 400 mg/dL. Apolipoprotein B concentration was measured by an immunonephelometric method.

Statistical Analysis

Statistical analysis was performed with the SAS Statistical Package (SAS Institute, Cary, NC) version 6.12 TS020. All differences between groups were evaluated using 2-tailed paired *t* tests. All categorical variables were analyzed using the χ^2 test.

RESULTS

Patients

A total of 118 patients were screened for the study. A total of 72 patients satisfied the inclusion/exclusion criteria and entered the trial. Ninety-four percent of the patients completed the study; 4 patients were not considered in the final analysis due to lack of compliance to the scheduled visits. These 4 patients were allocated to ciprofibrate; every patient was contacted, and no side effects caused withdrawal of the study. Of the remaining 68 patients, 32 received ciprofibrate 100 mg/d, and 36 were treated with gemfibrozil 1,200 mg/d. The baseline characteristics and measurements of patients are shown in Table 1. The 2 groups were comparable at baseline with respect to demographic characteristics and lipid parameters.

Table 1. Baseline Characteristics of All Patients Included in Study (n = 68)

Variable	Ciprofibrate (n = 32)	Gemfibrozil (n = 36)
Sex		
Male	14	22
Female	18	14
		Mean ± SD
Age (yr)	48.2 ± 9.7	49.6 ± 10.1
Weight (kg)	72 ± 12	70 ± 10
Height (cm)	161 ± 8	158 ± 6
Fasting plasma glucose (mg/dL)	94 ± 11	93 ± 9
TSH (mU/mL)	2.04 ± 0.7	2.3 ± 1.5

Efficacy

Both treatments had a significant beneficial effect on the lipid profile, as shown in Tables 2 and 3. No statistically significant difference was found between the treatments. After 8 weeks of treatment, plasma triglyceride concentrations were decreased by 43.5% and 54% during ciprofibrate and gemfibrozil therapy, respectively ($P < .001$ when week 0 *v* 8 are compared withboth treatments). HDL-C concentrations were increased by 20.8% and 19.3%, respectively ($P < .001$). Apoprotein B concentrations, cholesterol, and very–low-density lipoprotein-cholesterol (VLDL-C) concentrations were also decreased by the study drugs (18.6%, 13.2%, and 30.9% during ciprofibrate and 44%, 13.8%, and 14.4% during gemfibrozil, respectively). Meanwhile, the effect of the drug was moderate on LDL-C (7.03% and 4.2%, respectively). A significant decrease in non–HDL-C resulted from both treatments (19% and 19.5%, respectively, $P < .05$). No statistically significant differences were observed between treatments.

The percent of patients in whom the treatment goals were achieved were analyzed for both treatments. Many cases normalize their triglyceride concentrations below 150 mg/dL (62% for ciprofibrate and 83% for gemfibrozil). In a large proportion of the subjects, an HDL-C concentration above 35 mg/dL was achieved (93% and 91%, respectively). However, as expected, an LDL-C lower than 130 mg/dL was attained in 24% and 22% of the patients treated with ciprofibrate and gemfibrozil, respectively.

Ciprofibrate significantly decreased fibrinogen concentration by 18.8%t (313 ± 86 *v* 254.6 mg/dL, $P < .05$). Fibrinogen was not modified during gemfibrozil therapy (330 ± 83 *v* 344 ± 77 mg/dL, not significant [NS]).

Adherence to the diet was similar in both groups; it was at least regular in all cases. Compliance to the pharmacologic therapy was higher than 80% in every case. The body weight remained constant in all patients. The alcohol and tobacco consumption were not modified during the study.

Table 3. Changes in Lipid Profile and Safety Laboratory Tests Between Baseline and Posttreatment Values

	Week 0	Week 8	Percent Change	*P*
Fibrinogen (mg/dL)				
Ciprofibrate	313 ± 86	254 ± 62	−18.8	<.001
Gemfibrozil	330 ± 83	344 ± 77	+4.3	NS
Apoprotein B (mg/dL)				
Ciprofibrate	177 ± 26	144 ± 25	−18.6	<.001
Gemfibrozil	173 ± 22	148 ± 30	−14.4	<.001
Non–HDL-C (mg/dL)				
Ciprofibrate	230.7 ± 36	186.3 ± 35	−19	<.001
Gemfibrozil	234.3 ± 28	188.6 ± 39	−19.5	<.001
AST (mU/mL)				
Ciprofibrate	25 ± 10	26 ± 10	3.8	NS
Gemfibrozil	23 ± 7	32 ± 17	39	NS
ALT (mU/mL)				
Ciprofibrate	26 ± 11	27 ± 14	3.8	NS
Gemfibrozil	24 ± 11	29 ± 14	20	NS
Lactic dehydrogenase (mU/mL)				
Ciprofibrate	147 ± 26	154 ± 27	4.7	NS
Gemfibrozil	151 ± 30	147 ± 35	−2.6	NS

Abbreviation: NS, not significant.

Table 2. Changes in Lipid Profile and Clinical Characteristics Between Baseline and Posttreatment Values

	Week −4	Week 0	Week 4	Week 8	Percent Change	*P*
Weight (kg)						
Ciprofibrate	72 ± 12	71 ± 12	70 ± 12	69 ± 13	−2.8	NS
Gemfibrozil	70.1 ± 10	69.6 ± 10.6	68.4 ± 10	68.5 ± 10.6	−1.2	NS
Cholesterol (mg/dL)						
Ciprofibrate	278 ± 31	271 ± 35	233 ± 27	235 ± 30	−13.2	<.001
Gemfibrozil	280 ± 37	274 ± 30	244 ± 38	236 ± 38	−13.8	<.001
Triglycerides (mg/dL)						
Ciprofibrate	427 ± 223	347 ± 198	196 ± 100	196 ± 95	−43.5	<.001
Gemfibrozil	359 ± 245	335 ± 137	166 ± 80	154 ± 70	−54	<.001
HDL-C (mg/dL)						
Ciprofibrate	40.3 ± 15	40.3 ± 8.6	48.5 ± 12	48.7 ± 11.8	+20.8	<.01
Gemfibrozil	38.6 ± 7.2	39.7 ± 8	47.6 ± 8.2	47.4 ± 8.7	+19.3	<.001
LDL-C (mg/dL)						
Ciprofibrate	162.8 ± 39	163.8 ± 36	143 ± 24	149 ± 33	−9.7	NS
Gemfibrozil	175 ± 33	165 ± 32	162 ± 36	158 ± 39	−4.2	NS

Abbreviation: NS, not significant.

Safety

Liver function tests were not modified by either treatment (Table 3). No patient had a significant modification on any of the safety laboratory tests. There were no incidents of neither myopathy nor liver dysfunction. No persistent elevations in ALT, AST, or CPK, defined as potentially clinically relevant, were reported during the course of the study. None of the symptoms registered during the trial was related to the study drugs. The most frequently reported symptom was dizziness (4 cases in the ciprofibrate group and 1 in the gemfibrozil group).

DISCUSSION

Mixed hyperlipidemia is 1 of the more difficult dyslipidemias to treat because of the need to decrease simultaneously abnormally high levels of both plasma triglycerides and cholesterol.[1] The dyslipidemia is caused by the plasma accumulation of usually more than 1 kind of atherogenic lipoprotein[18]; the coexistence of several potentially atherogenic defects possibly explains the increased coronary risk observed in epidemiologic studies.

The results reported here are a good example of the therapeutic response to fibrates of patients with mixed hyperlipidemia. A significant improvement in plasma triglycerides and HDL-C concentrations resulted from the administration of both drugs, ciprofibrate and gemfibrozil. No statistically significant differences were found between the treatments. Our results are in accordance with previous reports.[19] Bruckert et al[19] compared the safety and efficacy of ciprofibrate (100 mg daily) and gemfibrozil (900 mg daily) in type IIa and IIb hyperlipidemias. No difference in the effects of the drugs on triglycerides and HDL-C was found.

In this report, the majority of the patients reached the therapeutic goals for HDL-C. More than 90% of cases normalized their HDL-C at the end of the trial. A reduction in the apolipoprotein B, VLDL-C, and non–HDL-C concentrations were observed. However, as expected, the LDL-C concentrations were not significantly modified by the fibrates. Only a small percentage of the cases (16.4% *v* 12.6% for ciprofibrate and gemfibrozil, respectively) have normal levels of apoprotein B or non–HDL-C at the end of the trial. These data clearly show that complete normalization of the lipid profile could be achieved in the mixed hyperlipidemia cases using a fibrate for 2 months. However, to attain the therapeutic goals suggested by the most recently published consensus,[20] these data suggest that a significant proportion of cases might need the addition of a statin.

The use of statins for the treatment of mixed hyperlipidemia results in less than ideal lipid reductions. Farnier et al[21] recently compared the actions of several doses of cerivastatin witht gemfibrozil. The fibrate decreased apoprotein B concentrations in the same magnitude (21.3%) as the highest dose (0.3 mg/d) of cerivastatin. As expected, the triglyceride reduction was significantly higher during gemfibrozil (50.3% *v* 20.3% at 0.3 mg/d of cerivastatin), but the LDL change was higher after the statin (23.6% *v* 8.2%). Unfortunately, the investigators did not present the percent of patients who achieved the therapeutic goals, but based of the baseline concentrations of plasma triglycerides (276 $\pm$ 80 mg/dL) and LDL-C (200 $\pm$ 30 mg/dL), only few cases may have attained it. Our results are very similar to the response observed after gemfibrozil therapy by Farnier et al.[21] These data show the potential need for combination therapy (statin plus fibrate) in a significant percent of patients with mixed hyperlipidemia.[22-26] Although, in the past, use of statin-fibrate combinations was limited because of reports of increased risk of myopathy, growing evidence indicates that statin-fibrate combinations can be used safely for prolonged periods.[22] Two long-term studies (one 3-year and one 4-year study) designed to assess the safety of this combination proved the lack of significant muscle or liver toxicity of the treatment.[27,28]

The different effects observed in this report on LDL-C, apoprotein B, and non–HDL-C concentrations seem to be, in some way, discrepant. However, the results may be caused by the limitations of using LDL-C as the main parameter of efficacy in mixed hyperlipidemia subjects.[29] Some accumulation of almost every subclass of the apoprotein B containing lipoproteins could be shown in these cases. The LDL-C concentrations underestimate the risk, because this parameter only represents a proportion of the lipoproteins accumulated in the plasma.[30] We believe that the apoprotein B concentration gives a more appropriate estimation of the risk and the effects of the treatment. Also, non–HDL-C concentrations could be used as an alternative.[20,31] In accordance with these statements is the observation that in several studies,[32,33] LDL-C was an independent predictor for cardiovascular mortality only in subjects with fasting triglycerides below 400 mg/dL, non–HDL-C remained the significant predictor even after inclusion of the hypertrygliceridemic subjects. Based on this evidence, non–HDL-C and/or apoprotein B concentrations could be considered the primary efficacy parameter, instead of LDL-C, in patients with mixed hyperlipidemia.

In this report, the efficacy of ciprofibrate and gemfibrozil for the treatment of mixed hyperlipidemia was compared in a group of patients carefully selected for similar lipid profiles. This approach limits the variability of responses due to the baseline characteristics of the population. Possible limitations of the study include the lack of family lipid profiles and apoE genotyping of the study patients. However, it is very unlikely that dysbetalipoproteinemia was a major cause of mixed hyperliperlipidemia in this population. This statement is based on the almost complete absence of the apo e2 allele in the Mexican population[34,35] and the poor LDL response observed with both drugs in our patients. In this homogeneous population, the effects of treatments on the lipid profile were remarkably similar. The only significant difference was observed in the ability of ciprofibrate to reduce fibrinogen concentration.[36] Fibrinogen has been found as an independent predictor for cardiovascular mortality in several studies,[37,38] but still it remains to be shown that lowering fibrinogen concentrations decreases the number of coronary events.

In conclusion, ciprofibrate and gemfibrozil are well-tolerated and efficacious treatments for mixed hyperlipidemia. In this trial, significant reductions in triglycerides (around 50%), non–HDL-C (19%), and apolipoprotein B (18%) were achieved with both drugs. The HDL-C concentration was increased above 35 mg/dL in the majority of cases. A significant fibrinogen reduction was observed with the use of ciprofibrate treatment. These positive effects might improve the atherothrombotic process and induce a positive clinical effect.

REFERENCES

1. Gaw A: Evidence based approach for the management of mixed hyperlipidemia. Atherosclerosis 137:S97-S100, 1998 (suppl)
2. Aguilar-Salinas CA, Barrett PHR, Schonfeld G: Description of a kindred with familial combined hyperlipidemia with unusual kinetic abnormalities of the apolipoprotein B containing lipoproteins. Effects of pravastatin therapy. Arterioscler Thromb Vasc Biol 17:72-82, 1997
3. Bredie SJ, Demacker P, Stalenhoef F: Metabolic and genetic aspects of familial combined hyperlipidemias with emphasis on low-density lipoprotein heterogeneity. Eur J Clin Invest 27:802-811, 1997
4. Assmann G, Schulte H, Cullen P: New and classical risk factors —The Munster Heart Study (PROCAM). Eur J Med Res 2:237-242, 1997
5. Direccion General de Epidemiología, Instituto Nacional de la Nutricion Salvador Zubiran: Encuesta Nacional de Enfermedades Cronicas, Subsecretaria de Coordinacion y Desarrollo, Secretaria de Salud, Mexico, 1993
6. Kesäniemi YA: Serum triglycerides and clinical benefit in lipid lowering trials. Am J Cardiol 81:70B-73B, 1998
7. Grundy SM: Consensus Statement: Role of therapy with "statins" in patients with hypertriglyceridemia. Am J Cardiol 81:1B-6B, 1998
8. Fruchart JC, Brewer B, Leitersdorf E, et al: Consensus for the use of fibrates in the treatment of dyslipoproteinemia and coronary heart disease. Am J Cardiol 81:912-917, 1998
9. Schoongans K, Martin G, Staels B, et al: Peroxisome proliferator-activated receptors, orphans with ligands and functions. Curr Opin Lipidol 8:159-166, 1997
10. Rubins HB, Robins SJ, Collins D, et al: Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. Veterans Affairs High - Density Lipoprotein Cholesterol Intervention Trial Study Group. N Engl J Med 341:410-418, 1999
11. Ericsson C, Nilsson J, Grip L et al: Effect of bezafibrate treatment over five years on coronary plaques causing 20% to 50% diameter narrowing (The Bezafibrate Coronary Atherosclerosis Intervention Trial (BECAIT)). Am J Cardiol 80:1125-1129, 1997
12. Cattin L, Da-Col P, Feruglio F et al: Efficacy of ciprofibrate in primary type II and IV hyperlipidemia: The Italian Multicenter Study. Clin Ther 12:482-488, 1990
13. Betteridge DJ: Ciprofibrate: A profile. Postgrad Med J 69:S42-S47, 1993
14. Bruckert E, Dejager S, Chapman MJ: Ciprofibrate therapy normalizes the atherogenic low-density lipoprotein subspecies profile in combined hyperlipidemia. Atherosclerosis 100:91-102, 1993
15. Goa K, Barradell L, Plosker G: Bezafibrate. Drugs 52:725-753, 1996
16. Knipscheer H, de Valois C, van den Ende B, et al: Ciprofibrate versus gemfibrozil in the treatment of primary hyperlipidemia. Atherosclerosis 124:S75-S81, 1996 (suppl)
17. National Cholesterol Education Program (NCEP) Expert Panel: Summary of the second report of the NCEP expert panel on detection, evaluation and treatment of high blood cholesterol (adult treatment panel II). JAMA 209:3015-3023, 1993
18. Mancini J: Angiographic trials of lipid-lowering therapy: An update. Curr Opin Lipidol 6:379-385, 1995
19. Bruckert E, Gheron G, Dairou F: Comparaison de l'efficacité et de la tolérance du ciprofibrate et du gemfibrozil dans le traitement des hyperlipidemies de type Iia et de type IIb. Synthese Med 429:14-16, 1998
20. American Association of Clinical Endocrinologyst (AACE): AACE lipid guidelines. Endocr Pract 6:164-213, 2000
21. Farnier M, and the Cerivastatin Study Group: Cerivastatin in the treatment of mixed hyperlipidemia: The right study. Am J Cardiol 82:47J-51J, 1998
22. Athyros V, Papageorgiu A, Hatzikonstandinou HA, et al: Safety and efficacy of long term statin-fibrate combination in patients with refractory familial combined hyperlipidemia. Am J Cardiol 80:608-613, 1997
23. Ellen R, McPherson R: Long term efficacy and safety of fenofibrate and a statin in the treatment of combined hyperlipidemia. Am J Cardiol 81:60B-65B, 1998
24. Stein E, Lane M, Laskarzewski P: Comparison of statins in hypertriglyceridemia. Am J Cardiol 81:66B-69B, 1998
25. Betteridge J, Khan M: Review of the guidelines for management of dislipidemia. Baillieries Clin Endocrinol Metab 9:867-890, 1995
26. Kayikcioglu M, Özerkan F, Soydan I: Effectiveness and safety of alternate-day simvastatin and fenofibrate on mixed hyperlipidemia. Am J Cardiol 83:1135-1137, 1999
27. Feher MD, Foxton J, Banks D, et al: Long term safety of statin-fibrate combinations in the management of hypercholesterolemia in patients with coronary artery disease. Br Heart J 74:14-17, 1995
28. Smit JW, Jansen GH, de Bruin Tw, et al: Treatment of combined hyperlipidemia with fluvastatin and gemfibrozil, alone or in combination, does not induce muscle damage. Am J Cardiol 76:126A-128A, 1995
29. Frost P, Havel R: Rationale for use of non–high-density lipoprotein cholesterol rather than low-desnity lipoprotein cholesterol as a tool for lipoprotein cholesterol screening and assessment of risk and therapy. Am J Cardiol 81:26B-31B, 1998
30. Branchi A, Rovellini A, Torri A. et al: Accuracy of calculated serum low-density lipoprotein cholesterol for the assessment of coronary heart disease risk in NIDDM patients. Diabetes Care 21:1397-1402, 1998
31. Garg A: Treatment of diabetic dyslipidemia. Am J Cardiol 81:47B-51B, 1998
32. Frost PH, Davis BR, Burlando AJ, et al for SHEP Research Group: Serum lipids and incidence of coronary heart disease: Findings from the Systolic Hypertension in the Elderly program (SHEP). Circulation 94:2381-2388, 1996
33. Aguilar CA, Talavera G, Ordovas JM, et al: The apolipoprotein E4 allele is not associated with an abnormal lipid profile in a Native American population following its traditional lifestyle. Atherosclerosis 142:409-414, 1999
34. Gamboa R, Hernandez G, Hesiquio R, et al: Apolipoprotein E polimorphism in the Indian and Mestizo populations of Mexico. Hum Biol 72:975-981, 2000
35. Illingworth DR, Stein EA, Mitchel YB, et al: Comparative effects of lovastatin and niacin in primary hypercholesterolemia: A prospective trial. Arch Intern Med 154:1586-1595, 1994
36. Desager JP, Horsmans Y, Vandenplas C, et al: Pharmacodynamic activity of lipoprotein lipase and hepatic lipase, and pharmacokinetic parameters measured in normolipidaemic subjects receiving ciprofibrate or micronised fenofibrate therapy for 23 days. Atherosclerosis 124:S65-S73, 1996 (suppl)
37. Gershlick AH: Blood markers of cardiovascular disease. Eur Heart J 20:1443-1444, 1999
38. Harjai K: Potential new cardiovascular risk factors: Left ventricular hypertrophy, homocysteine, lipoprotein (a), triglycerides, oxidative stress and fibrinogen. Ann Intern Med 131:376-386, 1999