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Atorvastatin versus Bezafibrate in Mixed Hyperlipidaemia

Randomised Clinical Trial of Efficacy and Safety (the ATOMIX Study)

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Abstract

Objective: Combined hyperlipidaemia is a common and highly atherogenic lipid phenotype with multiple lipoprotein abnormalities that are difficult to normalise with single-drug therapy. The ATOMIX multicentre, controlled clinical trial compared the efficacy and safety of atorvastatin and bezafibrate in patients with diet-resistant combined hyperlipidaemia.

Patients and study design: Following a 6-week placebo run-in period, 138 patients received atorvastatin 10mg or bezafibrate 400mg once daily in a randomised, double-blind, placebo-controlled trial. To meet predefined low-density lipoprotein-cholesterol (LDL-C) target levels, atorvastatin dosages were increased to 20mg or 40mg once daily after 8 and 16 weeks, respectively.

Results: After 52 weeks, atorvastatin achieved greater reductions in LDL-C than bezafibrate (percentage decrease 35 vs 5; $p < 0.0001$), while bezafibrate achieved greater reductions in triglyceride than atorvastatin (percentage decrease 33 vs 21; $p < 0.05$) and greater increases in high-density lipoprotein-cholesterol (HDL-C) [percentage increase 28 vs 17; $p < 0.01$]. Target LDL-C levels (according to global risk) were attained in 62% of atorvastatin recipients and 6% of bezafibrate recipients, and triglyceride levels <200 mg/dL were achieved in 52% and 60% of patients, respectively. In patients with normal baseline HDL-C, bezafibrate was superior to atorvastatin for raising HDL-C, while in those with baseline

HDL-C <35 mg/dL, the two drugs raised HDL-C to a similar extent after adjustment for baseline values. Both drugs were well tolerated.

Conclusion: The results show that atorvastatin has an overall better efficacy than bezafibrate in concomitantly reaching LDL-C and triglyceride target levels in combined hyperlipidaemia, thus supporting its use as monotherapy in patients with this lipid phenotype.

Mixed or combined hyperlipidaemia (CHL) is a common dyslipidaemia characterised by raised cholesterol and triglyceride levels, usually associated with low levels of high-density lipoprotein-cholesterol (HDL-C).[1] Whether familial or sporadic, this lipid phenotype carries a high risk of premature coronary artery disease[2-4] and is variably influenced by age, sex, hormonal status, the amount of visceral fat, and lifestyle factors, underlining its metabolic complexity.[5] Nevertheless, overproduction of very low-density lipoprotein (VLDL) apolipoprotein B (apo B) is thought to be the major underlying defect.[1,5,6]

The aim of therapy in CHL should be to normalise the multiple lipoprotein abnormalities, but their heterogeneous nature makes this a difficult task. Dietary treatment alone is often insufficient, although substantial lowering of triglyceride levels may be achieved.[7] Hypolipidaemic drugs are usually indicated, but the most appropriate therapy remains to be determined. Nicotinic acid decreases low-density lipoprotein-cholesterol (LDL-C) and triglycerides and increases HDL-C, but it often has disturbing adverse effects.[8] Bile acid sequestrants are poorly tolerated and may further increase triglyceride levels.[9] Fibric acid derivatives and HMG-CoA reductase inhibitors (statins) are frequently used in CHL. However, fibrates primarily lower triglycerides and increase HDL-C and may increase LDL-C.[10] On the other hand, statins reduce the LDL-C level but, at the usually recommended doses, have a limited capacity for lowering triglycerides and raising the HDL-C level.[11-18] Combined treatment with statins and fibrates may normalise the lipid profile, but there is concern about the safety of this approach.[19] Hence, there is a need for drugs that, as monotherapy, can safely lower both cholesterol and triglycerides and, hopefully, raise HDL-C as well.

The HMG-CoA reductase inhibitor atorvastatin reduces LDL-C by 41–61% over the dosage range of 10–80 mg/day, with greater efficacy than other drugs of the same class at the 10–40 mg/day dosage range.[20,21] In addition, atorvastatin reduces triglycerides by up to 46% in hypertriglyceridaemic patients.[22] The triglyceride-lowering efficacy of this drug has also been documented in patients with primary hypercholesterolaemia,[20,21] diabetes mellitus[23] and CHL.[24] The ATOrvastatin vs bezafibrate MIXed hyperlipidemia study (ATOMIX), a double-blind, randomised, multicentre clinical trial, was designed to compare the safety and lipid effects of atorvastatin 10–40 mg/day with those of the fibric acid derivative bezafibrate 400 mg/day in patients with diet-resistant CHL treated for 12 months.

Methods

Patients

Male and female patients (aged 18–80 years) with CHL were recruited from referrals to 25 hospital clinics in Spain and Portugal. An institutional review board at each centre approved the protocol, and written informed consent was obtained from all patients.

Patients were included in the trial if, after discontinuation of any lipid-regulating drug, formal dietary counselling and good compliance with the prescribed diet, and a 6-week placebo run-in period, they had a mean (of two consecutive analyses at weeks –4 and –2) level of triglycerides of <500 and ≥200 mg/dL in addition to LDL-C of <250 and >190, 180, 160 or 135 mg/dL, depending

on global risk status (low, moderate, high or presence of coronary heart disease, respectively), according to European Atherosclerosis Society (EAS) guidelines.[25]

Patients were ineligible if they had lipoprotein criteria diagnostic of dysbetalipoproteinaemia, were pregnant or nursing, had active liver disease or hepatic dysfunction (liver enzyme levels >2 times upper normal limits), nephrotic syndrome or renal insufficiency, hypothyroidism, body mass index ≥30 kg/m^2, known hypersensitivity to statins or fibrates, or excessive alcohol consumption.[25] Patients with uncontrolled hypertension or type 2 diabetes mellitus (HbA_{1c} >8%) and those with a cardiovascular event resulting in hospitalisation during the previous 3 months or major cardiovascular surgery during the preceding 6 months were also excluded. Medications known to affect lipid levels or to interact with study medications were not allowed. The dosage and regimen of any long-term, permitted concurrent medication was stabilised before the placebo baseline phase. Dietary compliance was assessed at baseline, and non-compliant patients were also excluded. Drug compliance was assessed by pill count.

Design

This was a 1-year, double-blind, randomised, multicentre clinical trial to evaluate the efficacy and safety of atorvastatin 10–40 mg/day compared with that of bezafibrate in a fixed dosage of 400 mg/day on plasma lipid and lipoprotein levels in patients with CHL. The study was divided into three phases: an initial 6-week placebo baseline phase, followed by a 16-week titration phase and a 36-week follow-up period.

All registered patients were instructed to follow the dietary recommendations of the Spanish Atherosclerosis Society,[26] which limit total fat to <35% of daily energy, saturated fatty acids to <10%, simple sugars to <10% and cholesterol to <300 mg/day. Compliance with diet was assessed before randomisation by a food frequency questionnaire and a 3-day dietary record. The nutrient composition of the diets was calculated with the Food Processor Plus, Version 5.0 software (ESHA Research, Salem, Oregon, USA), adapted to nutrient databases of specific Mediterranean foods when appropriate. Noncompliance was defined as a deviation of ≥20% of dietary instructions regarding main nutrient intake. All dietary records were analysed and scored by expert dietitians at a single reference centre (Lipid Clinic, Nutrition & Dietetics Service, Hospital Clinic, Barcelona), and the individual dietary assessments, including the need to exclude any patient from the study for lack of dietary compliance, were communicated to the investigators.

Qualifying patients were randomly assigned to receive either atorvastatin 10mg or bezafibrate 400mg (slow release) once daily, together with matching placebo. The allocation sequence was derived from a computer-generated randomisation list prepared by the central statistician (JMS) and was concealed in sealed envelopes with codes matching those of active drug and placebo containers. All investigators and participants were blinded to treatment assignment for the duration of the study. After 8 and 16 weeks, the dose of atorvastatin (or matching placebo) could be doubled according to EAS LDL-C target guidelines (LDL-C ≤175, 155, 135 or 100 mg/dL for patients at low, moderate or high risk or with coronary heart disease, respectively).[25] If after two consecutive titrations LDL-C levels were still above target at week 26, open-label colestipol (three sachets of 5 g/day) was recommended for the rest of the study in both arms. Lipid values were kept blind for both patients and investigators until the end of the study. The central laboratory sent notes to centre coordinators specifying the need to upgrade intervention or obtain repeated laboratory determinations for safety purposes, when necessary, but lipid values remained masked. Titration visits were scheduled 3–5 days after blood sampling. To evaluate dietary compliance throughout the study, two more 3-day dietary records were obtained from each patient at weeks 26 and 52.

Laboratory Determinations

Venous blood samples were taken after a 12-hour fast and were shipped on the same day to a central laboratory in Madrid, Spain, for lipid and apolipoprotein analysis (UNE-EN ISO9002:1994 certified by SGS ICS Ibérica). Cholesterol and triglycerides were measured in serum with commercial enzymatic kits (Boehringer Mannheim, Mannheim, Germany) adapted to the RA-XT autoanalyser (Bayer Diagnostics, Tarrytown, USA). β-Quantification was performed on samples from all patients to determine the lipoprotein profile according to established methods.[27] Apo B and apo A-I levels were measured in whole serum by immunoturbidimetry (Roche Diagnostica, Basel, Switzerland).

Safety Evaluation

Physical examinations and full chemistry and haematology evaluations were performed at screening and at weeks 0, 26 and 52 throughout the study in all randomised patients. A verified laboratory abnormality occurring during the study was reported as an adverse event and followed until resolution. When the serum levels of liver enzymes or creatine phosphokinase increased to >3 or >5 times the upper normal limits, respectively, the patient was scheduled for a repeat laboratory measurement. If the anomaly was confirmed, the medication was interrupted and enzyme levels were rechecked at 1-week intervals until they returned to pretreatment levels. Once values returned to baseline, medication could be reinstituted at the same dose level. Adverse events were recorded at each clinic visit and up to 15 days after cessation of treatment, using a modified COSTART dictionary.

Statistical Analysis

The sample size was calculated to provide a 90% power to detect a 10% difference between treatments in percentage change from baseline LDL-C at 26 weeks, based on a two-sided t-test at a 5% level of significance. Analysis of covariance was performed to compare the effects of atorvastatin and bezafibrate in terms of percentage change from baseline in the primary outcome (LDL-C level at 26 weeks) and secondary outcomes (all lipid variables at 52 weeks). Baseline lipid values were the average of three measurements at weeks –4, –2 and 0, and final values were the average of the last two measurements (weeks 24 and 26, and weeks 50 and 52). The model included the effects resulting from treatment, centre and baseline values as covariates. Version 6.12 of SAS was used for analysis and summarisation.

A modified intent-to-treat (MITT) analysis was performed with data from patients who were randomised to treatment, met the pre-established diagnostic criteria for inclusion, were known to take at least one dose of the drugs tested, and provided any follow-up data for LDL-C. For all groups of response to treatment, the last double-blind observation was carried forward for patients who did not have week 52 data.

Results

Patient Characteristics

Of 405 eligible patients screened, 138 were randomly assigned to treatment with either atorvastatin or bezafibrate, and 122 completed the trial (figure 1). The principal reason for not randomly assigning 267 patients was lack of qualification of entry lipid criteria after the diet-controlled 6-week placebo period, usually because LDL-C and/or triglyceride levels were reduced with diet. The 134 patients available after the first evaluation at week 8 were considered for the MITT analysis.

The baseline characteristics of these 134 patients are shown in table I. The patients studied were fairly representative of a high-risk population with CHL, namely, predominantly male, with a substantial proportion of patients with coronary heart disease, and disclosing elevated serum concentrations of total cholesterol, LDL-C and VLDL-C, total and VLDL triglycerides, and apo B, together with low HDL-C and apo A-I levels.

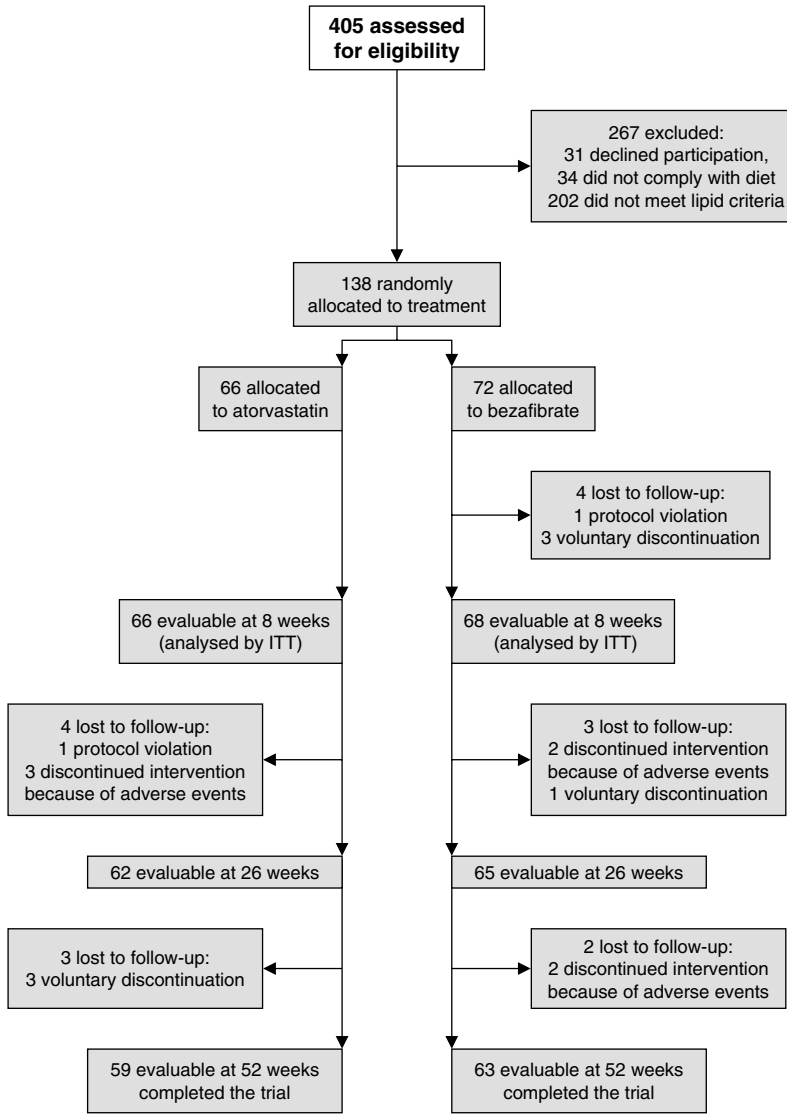

Fig. 1. Flow of participants in the trial. **ITT** = intention-to-treat.

Average triglyceride values were 25 mg/dL lower in the atorvastatin group than in the bezafibrate group. Although random assignment prevents selection bias, it does not guarantee that the groups are equivalent at baseline.[28] Any influence of the unequal distribution of triglyceride values on the

Table I. Characteristics of patients at baseline[a]

Variable	Atorvastatin (n = 66)	Bezafibrate (n = 68)
Age (y)	51 ± 11	53 ± 10
Body mass index (kg/m^2)	27.67 ± 1.93	27.43 ± 1.89
Males [no. (%)]	55 (83)	44 (65)
Smokers [no. (%)]	26 (39)	19 (28)
Diabetes [no. (%)]	6 (9)	7 (10)
Hypertension [no. (%)]	27 (41)	38 (56)
Risk classification		
Low risk [no. (%)]	1 (1)	0 (0)
Moderate risk [no. (%)]	1 (1)	1 (1)
High risk [no. (%)]	44 (67)	44 (65)
Coronary heart disease [no. (%)]	20 (30)	23 (34)
Lipid values[b]		
Total cholesterol (mg/dL)	282 ± 30	279 ± 29
LDL-C (mg/dL)	191 ± 25	184 ± 24
HDL-C (mg/dL)	37.8 ± 7.2	39.1 ± 6.6
HDL-C <35 mg/dL [no. (%)]	26 (39)	18 (26)
VLDL-C (mg/dL)	49.9 ± 17.5	52.6 ± 16.2
Triglycerides (mg/dL)	268 ± 68	293 ± 74
VLDL triglycerides (mg/dL)	168 ± 53	187 ± 58
Apolipoprotein B (mg/dL)	158 ± 20	155 ± 20
Apolipoprotein A-I (mg/dL)	131 ± 17	135 ± 18
Total cholesterol/HDL-C	7.8 ± 1.7	7.3 ± 1.1
LDL-C/HDL-C	5.3 ± 1.3	4.8 ± 0.8

a Data given as mean ± SD unless otherwise specified.

b To convert total, LDL-C, HDL-C and VLDL-C from mg/dL to mmol/L, multiply by 0.02586; to convert triglycerides and VLDL triglycerides from mg/dL to mmol/L, multiply by 0.1129.

HDL-C = high-density lipoprotein-cholesterol; **LDL-C** = low-density lipoprotein-cholesterol; **VLDL-C** = very low-density lipoprotein-cholesterol.

results was corrected by appropriate adjustment for baseline triglycerides using analysis of covariance (ANCOVA).

Dietary Analysis

The dietary records of each patient were evaluated at baseline and at 26 and 52 weeks. Thirty-four candidates were removed before treatment assignment because of gross noncompliance with dietary recommendations (figure 1). The demographic, anthropometric and serum lipid characteristics of this subgroup of patients were not different from those of the 138 patients assigned to treatment (data not shown). Overall dietary compliance was good throughout the study in the two treatment groups. The nutrient composition of the actual diets was similar at baseline and during the study for the two groups (data not shown).

Efficacy Analysis

The mean percentage changes in the primary outcome (LDL-C level at 26 weeks) were –36% in the atorvastatin group ($p < 0.0001$ vs baseline) and –0.5% in the bezafibrate group ($p = 0.80$ vs baseline).

Table II shows the values in lipid variables for atorvastatin and bezafibrate at 52 weeks. There were significant changes in the lipid profile from the placebo baseline for each drug and between the two drugs. Bodyweight changes from baseline at week 52 were both insignificant and similar in the two therapeutic groups (1% increase in each group). As shown in figure 2, atorvastatin treat-

ment produced adjusted mean decreases of LDL-C, total cholesterol and apo B levels and of the ratios total cholesterol/HDL-C and LDL-C/HDL-C that were significantly greater ($p < 0.0001$ for all) than those induced by bezafibrate (35% vs 5%, 28% vs 7%, 30% vs 12%, 38% vs 26% and 44% vs 24%, respectively). On the other hand, treatment with bezafibrate led to significantly ($p < 0.05$) greater reductions of total triglyceride and VLDL triglyceride levels than those observed after atorvastatin therapy (33% vs 21% and 42% vs 21%), while the decrease in the VLDL-C level was similar with the two drugs (38% vs 32%). As expected, bezafibrate was superior to atorvastatin in increasing HDL-C and apo A-I levels (28% vs 17% [$p < 0.01$] and 12% vs 7% [$p < 0.05$]).

At week 26, 52% of patients treated with atorvastatin reached the LDL-C goal compared with 3% of patients treated with bezafibrate ($p < 0.0001$). Figure 3 shows that, at the end of the study, 62% of patients given atorvastatin attained the LDL-C goal compared with only 6% of those given bezafibrate ($p < 0.0001$). When stratified by risk factors and, therefore, by LDL-C goals, the percentage of atorvastatin-treated patients reaching LDL-C target levels at 52 weeks increased to 75% in the high-risk group. Regarding triglyceride goals (<200 mg/dL) at 52 weeks, no differences

Table II. Effects of atorvastatin and bezafibrate on low-density lipoprotein-cholesterol (LDL-C) at 26 weeks and on lipid variables at 52 weeks by modified intention-to-treat analysis[a]

Variable	Atorvastatin	Bezafibrate	Treatment effect; mean difference between treatments (95% CI)
	mean measurements during treatment ± SD		
Primary endpoint			
LDL-C at 26 weeks (mg/dL)[b]	119 ± 30	184 ± 27	65 (56–74)
Secondary endpoints (lipid values at 26 weeks)[b]			
Total cholesterol (mg/dL)	198 ± 36	265 ± 32	67 (55–77)
HDL-C (mg/dL)	44 ± 8	49 ± 7	5 (3–8)
VLDL-C (mg/dL)	34 ± 17	29 ± 16	–5 (–10 to 0.6)
Triglycerides (mg/dL)	224 ± 82	178 ± 74	–46 (–70 to –21)
VLDL triglycerides (mg/dL)	148 ± 65	99 ± 58	–49 (–67 to –29)
Apolipoprotein B (mg/dL)	106 ± 22	138 ± 20	32 (25–38)
Apolipoprotein A-I (mg/dL)	140 ± 18	149 ± 16	9 (4–15)
Total cholesterol/HDL-C	5 ± 1	6 ± 1	1 (0.5–1.3)
LDL-C/HDL-C	3 ± 1	4 ± 1	1 (0.8–1.4)
Secondary endpoints (lipid values at 52 weeks)[b]			
LDL-C (mg/dL)	120 ± 31	176 ± 28	56 (46–65)
Total cholesterol (mg/dL)	200 ± 38	259 ± 34	59 (48–71)
HDL-C (mg/dL)	45 ± 9	49 ± 8	4 (2–7)
VLDL-C (mg/dL)	34 ± 20	32 ± 18	–2 (–8 to 4.2)
Triglycerides (mg/dL)	218 ± 100	189 ± 90	–29 (–59 to 1)
VLDL triglycerides (mg/dL)	140 ± 75	106 ± 67	–34 (–57 to –12)
Apolipoprotein B (mg/dL)	109 ± 23	137 ± 21	28 (21–35)
Apolipoprotein A-I (mg/dL)	142 ± 19	149 ± 17	7 (1–12)
Total cholesterol/HDL-C	5 ± 1	6 ± 1	1 (0.5–1.3)
LDL-C/HDL-C	3 ± 1	4 ± 1	1 (0.7–1.3)

a All values are adjusted for baseline values.

b To convert total, LDL-C, HDL-C and VLDL-C from mg/dL to mmol/L, multiply by 0.02586; to convert triglycerides and VLDL triglycerides from mg/dL to mmol/L, multiply by 0.1129.

HDL-C = high-density lipoprotein-cholesterol; **LDL-C** = low-density lipoprotein-cholesterol; **VLDL-C** = very low-density lipoprotein-cholesterol.

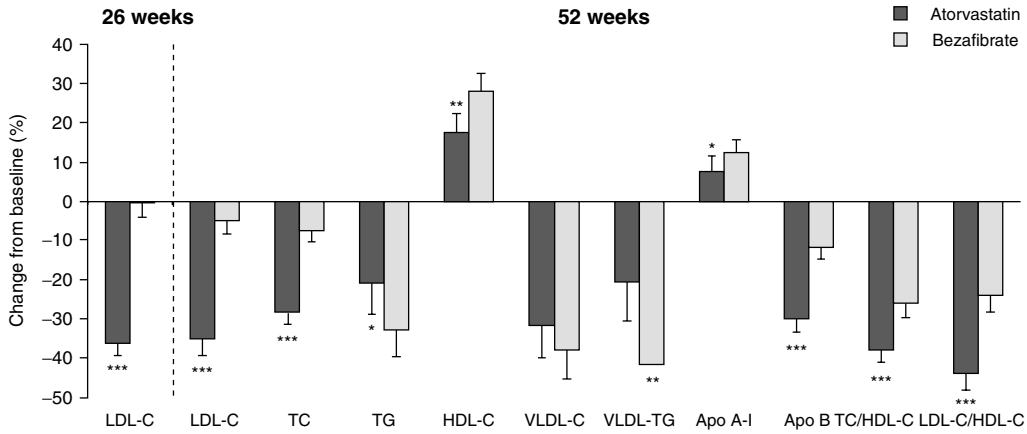

Fig. 2. Percentage changes from baseline in primary and secondary outcomes. Low-density lipoprotein-cholesterol (LDL-C) changes at 26 weeks (primary outcome) and lipid changes at 52 weeks (secondary outcomes) in patients treated with atorvastatin or bezafibrate. Adjusted mean percentage decreases (and 95% confidence intervals) at weeks 26 and 52 are shown. Modified intention-to-treat analysis with values for percentage change based on a covariance model with effects resulting from treatment, centre and baseline value as covariates.
Apo = apolipoprotein; **HDL-C** = high-density lipoprotein-cholesterol; **TC** = total cholesterol; **TG** = triglyceride; **VLDL-C** = very low-density lipoprotein-cholesterol; **VLDL-TG** = very low-density lipoprotein triglyceride. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.0001$, atorvastatin vs bezafibrate.

were observed between atorvastatin and bezafibrate (52% and 60%, respectively).

By the end of the study, the mean dosage of atorvastatin given was 23.5 mg/day, with 32% of patients taking 10 mg/day, 35% taking 20 mg/day and 33% taking 40 mg/day. Fewer than 10% of the patients in the atorvastatin group were taking colestipol at the end of the study, as opposed to 48% of those in the bezafibrate group. The reason for the lack of compliance with colestipol in many patients in the bezafibrate group was discontinuation of the drug as a result of poor tolerance prior to the final visit. Inasmuch as the average actual intake was less than one 5g sachet per day, compliance also was poor in those still taking colestipol at week 52. In patients taking bezafibrate alone the LDL-C level decreased by 2%, while it decreased by 8% in patients taking combined bezafibrate-colestipol treatment; this difference was nonsignificant ($p = 0.197$). Drug efficacy on triglyceride treatment goals (<200 mg/dL) at week 52 was evaluated in patients with and without added colestipol treatment (70% and 51%, respectively; $p = 0.124$) . No differences were observed on the attainment of triglyceride goals

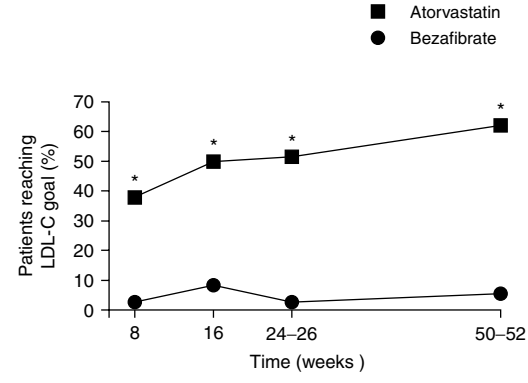

Fig. 3. Percentage of patients achieving low-density lipoprotein-cholesterol (LDL-C) target levels at specified times. LDL-C target levels were based on global risk, according to European Atherosclerosis Society guidelines.[25] Modified intention-to-treat analysis. * $p < 0.0001$, atorvastatin vs bezafibrate.

between patients taking bezafibrate alone and those taking added colestipol (70% and 51%, respectively; p = 0,124). Likewise, there were no differences in reaching triglyceride goals between patients taking atorvastatin alone and those treated with atorvastatin plus colestipol (52% and 50%, respectively; p = 0.938).

A subgroup analysis was performed to evaluate the effect of the two treatment modalities on HDL-C and apo A-I levels according to the baseline level of HDL-C ≥35 mg/dL (90 patients) or <35 mg/dL (44 patients). As shown in figure 4, atorvastatin was more effective in patients with low HDL-C than in those with normal HDL-C in raising the HDL-C (28% vs 11%; p = 0.0018) and the apo A-I level (13% vs 4%; p = 0.0125) and the HDL-C/apo A-I ratio (14% vs 7%; p = 0.0458), while the effect of bezafibrate was independent of baseline HDL-C levels. Both drugs were equally effective in raising HDL-C and apo A-I levels in patients with baseline HDL-C <35 mg/dL. Drug effects on HDL-C were unrelated to smoking status (data not shown).

Safety

The incidence of adverse events was 6.1% in the atorvastatin group and 12.5% in the bezafibrate group. Three patients given atorvastatin and four treated with bezafibrate withdrew because of adverse events, either associated or not with the study medication (figure 1). Relevant adverse events considered to be associated with drug therapy were insomnia (two patients) and elevated liver enzymes (one) in the atorvastatin group, and elevated liver enzymes (two) and elevation of creatine phosphokinase (one) in the bezafibrate group.

Discussion

In this multicentre, randomised clinical trial of 1-year duration, 138 patients with CHL under

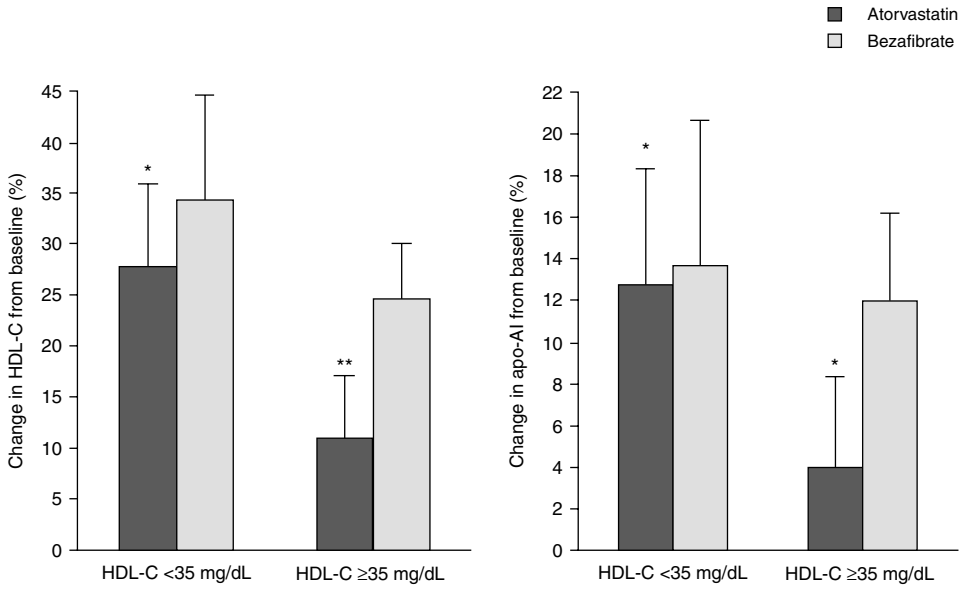

Fig. 4. Percentage changes of high-density lipoprotein-cholesterol (HDL-C) [**left panel**] and apolipoprotein (apo) A-I (**right panel**) according to baseline HDL-C levels. Changes at 52 weeks in patients treated with atorvastatin (26 with HDL-C <35 mg/dL and 40 with HDL-C ≥35 mg/dL) or bezafibrate (18 with HDL-C <35 mg/dL and 50 with HDL-C ≥35 mg/dL). Data are means and 95% confidence intervals. Modified intention-to-treat analysis. * p < 0.015 baseline HDL-C <35 mg/dL vs baseline HDL-C ≥35 mg/dL; ** p < 0.005 atorvastatin vs bezafibrate.

close dietary supervision received atorvastatin or bezafibrate as lipid-regulating agents. As expected from the mechanisms of action of these drugs, atorvastatin effectively lowered total cholesterol, LDL-C and apo B levels, whereas bezafibrate was most efficacious in lowering triglyceride-rich lipoproteins and raising HDL-C and apo A-I levels. However, even though bezafibrate was superior in this respect, atorvastatin significantly lowered triglycerides and raised the HDL-C and apo A-I levels as well. On the other hand, bezafibrate had only a marginal effect on elevated LDL-C. Furthermore, both drugs lowered VLDL-C levels to a similar extent. Finally, atorvastatin decreased the LDL-C/HDL-C ratio, an indicator of overall cardiovascular risk, nearly twice as much as bezafibrate.

Particular attention was given to dietary treatment in this trial, to the point that nearly two out of every four screened patients who initially fulfilled entry criteria were excluded during the diet-controlled placebo run-in period because target LDL-C or triglyceride levels were attained. Compliance with lipid-lowering diet was also ensured throughout the trial. Therefore, our patients, drawn from a high-risk population, had a truly diet-resistant, severe CHL phenotype.

In this trial the lipid-modulating effects of bezafibrate were similar to those reported for gemfibrozil or fenofibrate in other studies of patients with CHL,[11-17,24] falling short of the purported objective of normalising lipid levels because of the modest effect of fibrates on LDL-C. On the other hand, the substantial cholesterol-lowering effect of atorvastatin found in this study confirms previous observations.[20,24,29] Thus, 62% of patients were able to reach appropriate LDL-C target levels with atorvastatin, while this proportion was negligible with bezafibrate.

However, atorvastatin at a mean dosage of 23.4 mg/day (67% of the patients took daily doses of either 10 or 20mg) resulted in substantial reductions of triglyceride-rich lipoproteins, to the point that the percentage of patients achieving target triglyceride levels <200 mg/dL was similar to that obtained with bezafibrate. This effect was not unexpected given prior evidence of the hypotriglyceridaemic effect of atorvastatin,[22,24,29] but it had not been tested previously in a controlled manner in patients with CHL. The decrease in total triglyceride and VLDL components induced by atorvastatin treatment has been attributed to reduced VLDL synthesis and/or enhanced removal of triglyceride-rich remnant lipoproteins by way of increased LDL receptor expression.[30] Recently, Guerin et al.[31] have shown that the hypotriglyceridaemic effect of atorvastatin in CHL is associated with decreased cholesteryl ester transfer between lipoproteins and a substantial reduction in the proportion of small, dense LDL subspecies, thus providing an added antiatherogenic effect.

In spite of the substantial LDL-C- and triglyceride-lowering effects of atorvastatin shown in this study, almost 50% of patients thus treated failed to achieve target levels of both lipids, the desirable goal in CHL. It is well recognised that statin-fibrate combination regimens markedly ameliorate mixed lipid disorders such as CHL and may attain target levels of both LDL-C and triglycerides in a substantial majority of patients.[17,19,32] However, because of safety issues raised after the recent withdrawal of cerivastatin from the market, there has been an increasing concern about the risk of severe myopathy with any statin-fibrate combination treatment. The results of our study suggest that initial therapy with atorvastatin may suffice to attain target LDL-C and triglyceride values in CHL; if this is not the case, cautious addition of a fibric acid derivative such as bezafibrate may be tried with a good chance of normalising the lipid profile.

Low concentrations of HDL-C are strongly associated with an increased risk for coronary heart disease,[33] and raising them is an important target of therapeutic strategies in preventive cardiology.[34] In our study, HDL-C and apo A-I levels increased significantly with both drugs, with a greater overall effect of bezafibrate. However, a *post hoc* analysis of the influence of the baseline HDL-C level on drug-induced HDL-C and apo A-I changes after adjustment for sex and baseline tri-

glyceride levels showed that the increases with atorvastatin were more pronounced (and equalled those induced by bezafibrate) in patients who initially had HDL-C<35 mg/dL than in those with higher levels. This did not occur in patients given bezafibrate. Different findings, namely larger HDL-C increases with a fibrate drug (fenofibrate) than with atorvastatin in patients with low HDL-C, have been observed in a recent clinical trial.[35] Both dissimilar patient populations and atorvastatin doses might explain these discordant observations. Any formal demonstration of a differential effect of atorvastatin on HDL-C depending on baseline levels would require a clinical trial specifically designed to investigate this issue. However, recent evidence supports the concept that individuals with a low HDL-C level show a surprisingly good response to lipid-regulating agents.[36-40]

In the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial, treatment of patients with coronary heart disease and isolated low HDL-C with gemfibrozil increased the HDL-C level by 6% and reduced the recurrence of ischaemic events by 22%.[36] An additional analysis of the data of this trial revealed that HDL-C values at baseline and on-trial were inversely related to incident coronary heart disease, which was reduced by 11% with gemfibrozil treatment for every 5 mg/dL increase in HDL-C.[37] *Post hoc* analyses of clinical trials with HMG-CoA reductase inhibitors have also shown that participants with the lowest levels of HDL-C at baseline obtain most benefit from drug treatment in terms of coronary risk reduction[38] or angiographic progression of coronary artery disease.[39] Thus, both low baseline HDL-C and its on-treatment increase appear to define a subgroup of individuals whose high risk is reduced most by lipid-regulating therapy. The magnitude of drug-induced changes in the HDL-C level is of obvious importance. In the recently published HATS (HDL Atherosclerosis Treatment Study) trial[40] in patients with coronary heart disease and low HDL-C, combined simvastatin-nicotinic acid treatment led to LDL-C decreases and HDL-C increases of a similar magnitude to those observed with either atorvastatin or bezafibrate in our patients with low baseline HDL-C, and these changes were associated with marked clinical and angiographic benefits.

Conclusion

Even when administered at relatively low doses to high-risk patients with CHL, atorvastatin is well tolerated and effectively reduces both cholesterol-rich and triglyceride-rich lipoproteins. It achieves LDL-C and triglyceride target levels in a substantial proportion of patients while raising the HDL-C level to a similar extent to bezafibrate in those with low HDL-C values at baseline. Therefore, this unique lipid-modulating profile makes atorvastatin a good present-day alternative for initial therapy of this highly atherogenic lipid phenotype. The intriguing observation of a marked HDL-C-raising effect of both atorvastatin and bezafibrate in patients with low baseline HDL-C deserves further investigation.

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