OBJECTIVE — This study evaluated the effect of a atorvastatin-fenofibrate combination on lipid profile, in comparison to each drug alone, in patients with type 2 diabetes and combined hyperlipidemia (CHL).

RESEARCH DESIGN AND METHODS — A total of 120 consecutive patients, who were free of coronary artery disease (CAD) at entry, were studied for a period of 24 weeks. These patients were randomly assigned to atorvastatin (20 mg/day, n = 40), micronized fenofibrate (200 mg/day, n = 40), or a combination of both (atorvastatin 20 mg/day plus fenofibrate 200 mg/day, n = 40). The effect of treatment on LDL cholesterol, triglycerides (TGs), HDL cholesterol, apolipoprotein A-I and B, lipoprotein(a), and plasma fibrinogen (PF) was recorded. Moreover, the percentage of patients that reached the American Diabetes Association treatment goals and the estimated CAD risk status were calculated.

RESULTS — No patient was withdrawn from the study because of side effects. The atorvastatin-fenofibrate combination reduced total cholesterol by 37%, LDL cholesterol by 46%, TGs by 50%, and PF by 20%, whereas it increased HDL cholesterol by 22% (P < 0.0001 for all). These changes were significantly better than those of both monotherapies. Of the patients on drug combination, 97.5% reached the LDL cholesterol treatment goal of <100 mg/dl, 100% reached the desirable TG levels of <200 mg/dl, and 60% reached the optimal HDL cholesterol levels of >45 mg/dl. These rates were significantly higher than those of both monotherapies. Combined treatment reduced the 10-year probability for myocardial infarction from 21.6 to 4.2%.

CONCLUSIONS — The atorvastatin-fenofibrate combination has a highly beneficial effect on all lipid parameters and PF in patients with type 2 diabetes and CHL. It improved patients’ CAD risk status significantly more than each drug alone.

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Atorvastatin and Micronized Fenofibrate Alone and in Combination in Type 2 Diabetes With Combined Hyperlipidemia

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Combined hyperlipidemia (CHL), a highly atherogenic lipid disorder characterized by increased LDL cholesterol, elevated triglycerides (TGs), and low HDL cholesterol, is not rare in patients with type 2 diabetes (1). Moreover, metabolic abnormalities, such as predominance of small dense LDL particles (2) and increased glycation of LDL (3), raise the atherogenic risk in these patients. Glycemic control appears to improve but not normalize these abnormalities (4). Statins or fibrates can be used in this setting. Statins have been shown to reduce atherosclerosis-related morbidity and mortality in patients with diabetes (5,6). On the other hand, fibrates are drugs that can decrease TG concentrations and elevate HDL cholesterol, thus reducing cardiovascular morbidity and mortality (7,8). Recent studies (9,10) showed that statin or fibrate monotherapies can improve the lipid profile in patients with type 2 diabetes and CHL; however, these affect different aspects of lipoprotein (LP) metabolism. Hence, it is difficult to modify the lipid profile of patients with type 2 diabetes and CHL using monotherapy with either a statin or a fibrate, according to the recent suggestions of the American Diabetes Association (ADA) (11).

An effective therapeutic approach of CHL in nondiabetic patients is a statin-fibrate combination (12–19). This regimen has not been widely adopted because of the concern about side effects, mainly myopathy, reported with the lovastatin-gemfibrozil combination (20). This has not been confirmed by studies using other statin-fibrate combinations (12–19). The recently reported problems with cerivastatin, when combined with gemfibrozil, seem to be related mainly to the toxicity of cerivastatin, because most deaths due to myopathy-rhabdomyolysis reported in the U.S. were associated with monotherapy rather than with combination therapy.

The present open-label prospective
randomized parallel study was undertaken to investigate the hypothesis that combination therapy with atorvastatin and micronized fenofibrate will be more effective than each drug alone in tackling multiple lipid coronary artery disease (CAD) risk factors in patients with type 2 diabetes and CHL.

**RESEARCH DESIGN AND METHODS** — The study included 120 consecutive patients with type 2 diabetes and CHL, who were free of CAD at baseline, with fairly adequate glycemic control. The inclusion criteria were no previous hypolipidemic treatment, HbA1c <8.5%, and laboratory findings of CHL. CHL was defined as total cholesterol (TC) >220 mg/dl (5.7 mmol/l), LDL cholesterol >130 mg/dl (3.4 mmol/l), TG from 200 mg/dl (2.3 mmol/l) to 399 mg/dl (4.5 mmol/l), HDL cholesterol <40 mg/dl (1.04 mmol/l), and apolipoprotein (apo) B >150 mg/dl. Patients were on the National Cholesterol Expert Panel step 2 hypolipidemic diet for 6 weeks, during which time they received a placebo tablet daily. After that, if they still met the inclusion criteria, they continued participating in the study. Fertile women were excluded. In all patients, normal liver and renal function was established. The study protocol received ethical approval, and informed consent was obtained by all participants before enrolment.

**Study design**

Patients were randomized into three groups, using the Random Number Generation, Discrete Uniform, Stat Graphics version 4.0 (Statistical Graphics, Princeton, NJ) method, and they were assigned to active treatment for 24 weeks with atorvastatin (20 mg/day, n = 40), micronized fenofibrate (200 mg/day, n = 40), or a combination of both (atorvastatin 20 mg/day plus micronized fenofibrate 200 mg/day, n = 40). Lipid profile assessment as well as physical and laboratory investigation for drug-induced adverse effects were performed every month. Hypoglycemic or other concurrent treatments remained unchanged throughout the study.

**Table 1** — Demographic characteristics and baseline values of measured parameters of the patients with type 2 diabetes and combined hyperlipidemia in the three treatment groups

<table>
<thead>
<tr>
<th></th>
<th>Atorvastatin group</th>
<th>Fenofibrate group</th>
<th>Combination group</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>40</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>23/17</td>
<td>22/18</td>
<td>23/17</td>
</tr>
<tr>
<td>Age (years)</td>
<td>57 (44–67)</td>
<td>58 (48–69)</td>
<td>58 (50–68)</td>
</tr>
<tr>
<td>Hypoglycemic treatment (oral/insulin)</td>
<td>16/24</td>
<td>18/22</td>
<td>17/23</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>8.1 ± 0.2</td>
<td>8.0 ± 0.3</td>
<td>8.1 ± 0.2</td>
</tr>
<tr>
<td>Duration of diabetes (years)</td>
<td>8.6 ± 1.6</td>
<td>8.9 ± 1.8</td>
<td>8.5 ± 1.6</td>
</tr>
</tbody>
</table>

Data are n, median (range), or means ± 1 SD.

**Assessments**

After an overnight fast, TC, TG, and uric acid were assessed by an Olympus AU 560 autoanalyzer, using respective reagents (Olympus Diagnostica, Clare, Ireland). LDL cholesterol was calculated by the Friedewald formula (in mg/dl) [LDL cholesterol = TC – (TG/5 + HDL cholesterol)]. Apo B and A-I values were assessed by the immunoprecipitin method with the Technicon RA-1000 autoanalyzer (Technicon-Swords, Dublin, Ireland), using the apo B and apo A-I reagents, respectively (Incstar, Stillwater, MN). Lp(a) levels were measured using a monoclonal anti–Lp(a) antibody technique and enzyme-linked immunoassay (Terumo Medical, Elkron, MD). Plasma fibrinogen (PF) was assessed with the Clauss method, using the fibrin titer test Fibrinex (Ortho Diagnostic, Raritan, NJ).

**Estimated risk for myocardial infarction**

The risk for myocardial infarction within the next 10 years, using the PROCAM risk calculator suitable for men and postmenopausal women (21 and online at http://www.chld-taskforce.de/), was calculated in all patients at baseline and during monotherapy or combination treatment.

**Statistics**

Results are reported as the means ± SD. ANOVA, with 95% CIs, was used to compare values within and between the treatment groups. Differences were considered to be significant at P < 0.05. Mean percent changes of the LP and apo values were also calculated. For all forms of statistical analysis, SPSS version 8.0 (SPSS, Chicago, IL) was used.

**RESULTS** — All 120 patients concluded the study: 68 men and 52 women, with an age range of 44–69 years (median 58). At baseline, there were no significant differences in the demographic characteristics of the three treatment groups (Table 1).

**Adverse effects**

No significant adverse events were recorded. There was a nonsignificant increase in serum transaminase values in patients on combination treatment. These remained under the threefold level of the upper normal limit. No patient presented myalgia or creatine kinase (CK) levels >10-fold from pretreatment values. CK was increased with combination treatment at a higher level than with both monotherapies, but it remained within the normal range. No patient was withdrawn from the study because of side effects.

**Glycemic control and lipid parameters**

HbA1c remained unchanged throughout the study in all groups. Combined treatment had a beneficial effect on all lipid parameters. It reduced TC and LDL cholesterol significantly more than atorvastatin, whereas it had a better effect on TG and HDL cholesterol than micronized fenofibrate (Table 2). Lp(a) levels were not affected by all three regimens.

**PF and uric acid**

Atorvastatin had a neutral effect on PF levels. Fenofibrate and drug combination reduced PF significantly (21 and 20%, respectively; P < 0.001 vs. baseline and P < 0.01 vs. atorvastatin) (Table 2). Uric acid was reduced by atorvastatin and drug combination (Table 2).

**Treatment goals**

According to the ADA recommendations (11), the goal for LDL cholesterol of <100 mg/dl (2.4 mmol/l), the desirable TG levels of <200 mg/dl (2.6 mmol/l), and the
optimal HDL cholesterol levels of >45 mg/dl (1.2 mmol/l) was reached with combination therapy by significantly more patients than with both monotherapies, with atorvastatin being the second best in reaching the LDL cholesterol goal and fenofibrate in reaching TG and HDL cholesterol targets (Table 3).

**Estimated risk for myocardial infarction**

The probability of having a myocardial infarction within the next 10 years in all patients at baseline was calculated at 21.6%. With atorvastatin this was reduced to 7.5% (P < 0.0001 vs. baseline, P < 0.05 vs. fenofibrate), and with fenofibrate it was reduced to 10.9% (P < 0.0001 vs. baseline), whereas with combination therapy it was reduced to 4.2% (P < 0.05 vs. both monotherapies and P < 0.0001 vs. baseline) (Table 3).

**CONCLUSIONS** — Both atorvastatin and fenofibrate significantly improved the lipid profile, each in different aspects, in this group of patients with type 2 diabetes and CHL. However, both monotherapies were not able to induce the maximum global change in patients’ CAD risk profile. Conversely, combined therapy had a concurrent beneficial effect on all lipid parameters, changing the CAD risk status of these patients from high to low. Until now, the effects of statins and fibrates in patients with type 2 diabetes and CHL were compared in a competitive manner. Results of this paper suggest that the combination treatment seems to be the optimal therapeutic approach.

The landmark survival trials with statins (the Scandinavian Simvastatin Survival Study [4S], Cholesterol and Recurrent Events [CARE] study, and Long-Term Intervention with Pravastatin in Ischemic Heart Disease [LIPID] trial for secondary as well as the West of Scotland Coronary Prevention Study [WOSCOPS] for primary CAD prevention) showed that considerable reduction in LDL cholesterol levels induces clear clinical benefit for high-risk patients. The biggest reduction in coronary mortality (42%) was induced by a 35% reduction in LDL cholesterol by simvastatin, in comparison to placebo, in the 4S (22). In this study, patients with diabetes in the original report (n = 202 with the old ADA criteria) were benefited more (55% reduction in coronary mortality) than nondiabetic patients (5). Even with the new (1997) ADA diagnostic criteria, the benefit was greater in patients with diabetes (n = 483) or impaired glucose tolerance (n = 678) than in nondiabetic patients (23). The LDL cholesterol reduction seen in the present study, by combined therapy and atorvastatin, were greater than in the 4S. Hopefully, this will translate into analogous clinical benefit.

The two hypolipidemic drugs used in the present study have complementary modes of action. Atorvastatin is a potent inhibitor of hydroxymethylglutaryl-CoA reductase, which decreases LDL cholesterol in plasma by upregulating LDL receptor activity (24). It has been shown that atorvastatin significantly reduced circulating levels of major LDL subspecies: light, intermediate, and dense (25); however, in terms of absolute LP mass, the reduction in small dense LDL particles and atherogenic LDL particles, characteristic of CHL, was predominant (26). Atorvastatin also reduces the secretion of apo B—containing LPs. This is believed to account for its TG-lowering effect (27), which is more profound at higher doses (28,29). Effects on apo E, C-II, and C-III and a dose-dependent reduction in cholesterol ester transfer protein activity by atorvastatin have also been suggested (26). Fenofibrate activates peroxisome proliferator–activated receptors (30),

### Table 2—Baseline values of measured parameters of the patients with type 2 diabetes and combined hyperlipidemia in the three treatment groups and effect of treatment

<table>
<thead>
<tr>
<th></th>
<th>Atorvastatin Group</th>
<th>Fenofibrate Group</th>
<th>Combination Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Treatment</td>
<td>Effect</td>
</tr>
<tr>
<td>TC</td>
<td>252 ± 17</td>
<td>174 ± 10*</td>
<td>−31</td>
</tr>
<tr>
<td>TGs</td>
<td>278 ± 24</td>
<td>195 ± 22*</td>
<td>−30</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>161 ± 15</td>
<td>97 ± 7*</td>
<td>−40</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>34 ± 3.2</td>
<td>37.7 ± 4.5*</td>
<td>9</td>
</tr>
<tr>
<td>Apo A-1</td>
<td>124 ± 10</td>
<td>127 ± 9</td>
<td>3</td>
</tr>
<tr>
<td>Apo B-100</td>
<td>169 ± 18</td>
<td>117 ± 11*</td>
<td>−31</td>
</tr>
<tr>
<td>Lp(a)</td>
<td>18.4 ± 3.7</td>
<td>18.8 ± 4.3</td>
<td>2</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>379 ± 30</td>
<td>369 ± 34</td>
<td>−3</td>
</tr>
</tbody>
</table>

Data are means ± 1 SD in mg/dl or %. *P < 0.0001 vs. baseline; †P < 0.05 vs. atorvastatin; ‡P < 0.05 vs. both monotherapies. To convert data from mg/dl to mmol/l, divide TC and LDL and HDL cholesterol values by 38.7 and TGs by 88.6.

### Table 3—Percentage of patients reaching lipid targets set by the ADA and percent probability for myocardial infarction within the next 10 years as estimated with the PROCAM CAD calculator (21)

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Atorvastatin</th>
<th>Micronized fenofibrate</th>
<th>Combination therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>120</td>
<td>40</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>ADA LDL cholesterol goal</td>
<td>0</td>
<td>80*†</td>
<td>5*</td>
<td>97.5*‡</td>
</tr>
<tr>
<td>TG desirable levels</td>
<td>0</td>
<td>75*</td>
<td>92.5*§</td>
<td>100*‡</td>
</tr>
<tr>
<td>HDL cholesterol optimal levels</td>
<td>0</td>
<td>17.5*</td>
<td>30*§</td>
<td>60*§</td>
</tr>
<tr>
<td>10-year probability for myocardial infarction</td>
<td>21.6</td>
<td>7.5*†</td>
<td>10.9*</td>
<td>4.2*‡</td>
</tr>
</tbody>
</table>

Data are %. *P < 0.0001 vs. baseline; †P < 0.05 vs. fenofibrate; ‡P < 0.05 vs. both monotherapies; §P < 0.05 vs. atorvastatin.
which induce an increase in LP lipase activity, a reduction in apo C-III, an increase in apo A-I, as well as a reduction in cholesterol ester transfer protein activity (31). These result in TG level reduction, redistribution of LDL particle size, and an HDL cholesterol increase. The significant reduction of apo B, with “low or normal” LDL cholesterol, seen in this study with atorvastatin, fenofibrate, and mainly with their combination is indicative of a beneficial increase in LDL particle size (15).

Statins should be the basis of treatment in diabetic dyslipidemia because they exhibit an excellent effect in reducing high LDL cholesterol, the main enemy, but they also display their pleotropic effects, which are valuable in high-risk patients. It has been shown that the higher doses of statins may be moderately effective at reducing TG levels (although not necessarily at raising HDL levels) and thus may reduce the need for combination therapy (11). Nonetheless, with the use of high doses of statins, the LDL levels may be reduced to <80 mg/dl, and there is no safety data at such low LDL levels (11). Besides, statin-fibrate combinations seem superior than high dosages of statins because they normalize all aspects of the lipid profile and further improve CAD risk status. The fibrate induced additional, but moderate, LDL cholesterol reduction, especially by fenofibrate (17), and the substantial reduction in TG levels, the shift to a less-dense and thus less-atherogenic LDL particle profile, as well as the significant increase in HDL cholesterol levels (32) substantially improve the efficacy of combination treatment. The Veterans Affairs High-Density Lipoprotein Intervention Trial (VA-HIT) (8) showed that treatment with gemfibrozil resulted in a significant elevation in HDL cholesterol and a reduction in TGs in patients with borderline TG at entry, with no change in LDL cholesterol, that coincided with a significant reduction in the CAD event rate (22%). On the other hand, in a subgroup of patients (n = 459) of the Bezafibrate Infarction Prevention (BIP) trial (7) with elevated baseline TG levels (>200 mg/dl), treatment with bezafibrate induced a significant reduction in the primary study end points (40%), which were related to significant reductions in TG and increases in HDL cholesterol, accompanied by a small decrease in LDL cholesterol. Fenofibrate and combination therapy in our patients induced an increase of HDL cholesterol and a reduction in TG levels significantly higher than that of the VA-HIT and the BIP trial. Hopefully, they will translate into analogous clinical benefit.

PF, an independent predictor of myocardial infarction in both sexes (33), remained unaffected by atorvastatin and was significantly reduced by fenofibrate and drug combination. Whether atorvastatin affects fibrinogen concentrations has been a matter of debate. The overall impression is that atorvastatin does not affect fibrinogen concentration if a controlled study design is used (34–36). Atorvastatin did not have any adverse effect on Lp(a) levels. This is consistent with the findings of a recent study (34). The beneficial effect of atorvastatin on uric acid levels has recently been reported (37).

The literature on statin-fibrate combinations in patients with type 2 diabetes and CHL is limited. Until now, only two studies addressing this issue have been published. One study (38) combining simvastatin (20 mg/day) and bezafibrate (400 mg/day) had moderate results in terms of TC (−23%) and LDL cholesterol (−29%) reduction, although drug combination significantly reduced TG levels by 42% and increased HDL cholesterol by 25%. Of the 148 patients from this study, 2 presented myopathy. An older study (39) compared gemfibrozil alone versus placebo and, in a second phase, versus the combination of gemfibrozil plus lovastatin in 16 patients with type 2 diabetes. Most of the patients (10) presented TG levels >500 mg/dl, despite good glycemic control. Differences in study populations do not permit comparison of our outcomes with those of the latter study. Our findings are consistent with those of another study (17) combining atorvastatin with fenofibrate in nondiabetic patients with severe CHL.

There are two ongoing trials on diabetic dyslipidemia: Fenofibrate Intervention and Event Lowering in Diabetes (FIELD), with micronized fenofibrate, and the Collaborative Atorvastatin Diabetes Study (CARDS), with atorvastatin. The Lipids in Diabetes Study (LDS), with micronized fenofibrate and cerivastatin alone or in combination, was prematurely terminated because of the withdrawal of cerivastatin. The FIELD and CARDS trials include primary prevention patients with type 2 diabetes and have clinical events as the primary end points, but they are still in early stages, and it will take them a few years to provide evidence on which to base medical treatment of diabetic dyslipidemia. In the meantime, there is an urgent necessity to have an effective drug regimen at hand for patients with type 2 diabetes and CHL. Data from the present study suggest that the atorvastatin-fenofibrate combination may serve this purpose.

**Study limitations**
The study was placebo controlled only in regard to baseline assessments, but not during the active treatment period because of ethical issues, and it was not double blind for practical reasons. The study was underpowered to prove the safety of the atorvastatin-fenofibrate combination.

**Summary**
The atorvastatin-fenofibrate combination is a very effective therapeutic approach of patients with type 2 diabetes and CHL. It has a clear beneficial effect on all lipid parameters and PF concentrations. These properties reduce CAD risk, expand the spectrum of therapeutic choices, and enhance the individualization of hypolipidemic treatment in patients with type 2 diabetes.

**References**
Atorvastatin plus fenofibrate in type 2 diabetes


