The Effect of Aggressive Versus Standard Lipid Lowering by Atorvastatin on Diabetic Dyslipidemia

The DALI Study: a double-blind, randomized, placebo-controlled trial in patients with type 2 diabetes and diabetic dyslipidemia

THE DIABETES ATORVASTATIN LIPID INTERVENTION (DALI) STUDY GROUP

OBJECTIVE — In patients with type 2 diabetes, intensive glucose regulation, although effective for microangiopathy, has not been shown to have unambiguous preventive effects on the occurrence of cardiovascular disease. Patients with diabetes show a characteristic dyslipidemia (high triglyceride level, low HDL cholesterol level). Aggressive reduction of triglycerides might be an effective method to reduce the cardiovascular risk in these patients.

RESEARCH DESIGN AND METHODS — A double-blind, placebo-controlled, randomized study to assess the effect of 30 weeks of administration of atorvastatin 10 and 80 mg on plasma triglyceride levels in 217 patients with type 2 diabetes and fasting triglyceride levels between 1.5 and 6.0 mmol/l.

RESULTS — Administration of atorvastatin 10 and 80 mg resulted in significant reductions (25 and 35%, respectively) of plasma triglyceride levels (both $P < 0.001$). The difference between 10 and 80 mg was not statistically significant ($P > 0.5$). Atorvastatin 10 mg provided significant reductions from baseline in total cholesterol (−30%, $P < 0.001$), LDL cholesterol (−40%, $P < 0.001$), and apolipoprotein B (−31%, $P < 0.001$), and significantly increased HDL cholesterol from baseline by 6% ($P < 0.005$). Atorvastatin 80 mg had a similar effect on HDL cholesterol (+5.2%, $P < 0.005$) but significantly decreased total cholesterol (−40%, $P < 0.001$), LDL cholesterol (−52%, $P < 0.001$), and apolipoprotein B (−40%, $P < 0.001$) more than atorvastatin 10 mg ($P < 0.005$). The side effects of atorvastatin 10 and 80 mg were similar and did not differ from the patients receiving placebo.

CONCLUSIONS — Administration of 10- and 80-mg doses of atorvastatin provides similar, significant reductions from baseline in triglyceride levels in patients with type 2 diabetes. A higher dose of atorvastatin improves cholesterol-related parameters. Both doses were well tolerated in this patient population.

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Patients with type 2 diabetes have a two- to fourfold increased risk for cardiovascular morbidity and mortality (1–5). Intensive glucose regulation in type 2 diabetes, although effective for microangiopathy, has not been shown to have unambiguous preventive effects on the occurrence of coronary heart disease, stroke, and peripheral artery disease (6). Besides hypertension, dyslipidemia has emerged as a prevalent and modifiable atherogenic risk factor in patients with type 2 diabetes. LDL cholesterol–lowering strategies, with the use of hydroxymethylglutaryl (HMG)-CoA reductase inhibitors, have shown at least equal benefits for subgroups of patients with diabetes in large secondary prevention trials (7–9). In primary prevention trials, the diabetic subgroups were too small to show significant results (10,11). However, these were all post-hoc analyses, and patients with diabetes included in these studies did not have the typical diabetic lipid profile, i.e., elevated triglyceride level, decreased HDL cholesterol, and normal or slightly increased LDL cholesterol (12). In patients with diabetes, increased plasma triglyceride levels are associated with an increased risk for cardiovascular morbidity and mortality (13–17). As a consequence, optimal lipid lowering in type 2 diabetes should focus on lowering of LDL cholesterol and plasma triglyceride levels (14,15). HMG-CoA reductase inhibitors have been proven to effectively reduce total cholesterol and triglycerides in nondiabetic patients (18,19). Only one small randomized study on the effect of different doses of simvastatin on diabetic dyslipidemia has been published (20). Because higher doses of statins are effective in more aggressive cholesterol lowering (19), we hypothesized that higher doses of statins also result in additional improvement of the diabetic lipid profile.

We performed a double-blind, placebo-controlled, randomized study to assess the effect of atorvastatin 10 mg (A10) and 80 mg (A80) on the reduction of triglyceride levels in patients with type 2 diabetes and diabetic dyslipidemia. In addition, we studied the effects on other aspects of diabetic dyslipidemia.

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Abbreviations: A10, atorvastatin 10 mg; A80, atorvastatin 80 mg; apoB, apolipoprotein B; DALI, Diabetes Atorvastatin Lipid Intervention; FFA, free fatty acid; HMG, hydroxymethylglutaryl; LPL, lipoprotein lipase.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

RESEARCH DESIGN AND METHODS

Patients

The Diabetes Atorvastatin Lipid Intervention (DALI) Study is a randomized

double-blind, placebo-controlled, multicenter study conducted in the Netherlands. Patients were recruited from outpatient clinics of the University Medical Centers of Leiden, Rotterdam, and Utrecht and surrounding community hospitals. The medical ethical committees of the three participating institutions approved the study, and written informed consent was obtained from all patients. The participants, aged 45–75 years, were male or female patients with type 2 diabetes with a duration of diabetes of at least 1 year and an HbA_{1c} level of 10% or lower. The main inclusion criteria were fasting total cholesterol level between 4.0 and 8.0 mmol/l and fasting triglyceride level between 1.5 and 6.0 mmol/l.

Patients were not included in the present study if they had a history of myocardial infarction, percutaneous transluminal coronary angioplasty, coronary artery bypass grafting, proven manifest coronary artery disease, severe or unstable angina pectoris (higher than grade II of the Canadian Cardiovascular Society), clinically manifest heart failure (higher than grade II New York Heart Association), or severe cardiac arrhythmia. Premenopausal women and patients with acute liver disease or hepatic dysfunction, impaired renal function (plasma creatinine >150 μmol/l), history of partial ileal bypass surgery, any surgical procedure or any systemic inflammatory disease within 3 months before randomization, malignancy, vasculitis, rheumatic arthritis, idiopathic lung fibrosis, ulcerative colitis, or Crohn's disease were excluded. Patients who consumed more than four alcoholic drinks per day or who used systemic steroids, androgens, cyclosporin, other immunosuppressive drugs, erythromycin, or mibefradil were also excluded. When applicable, lipid-lowering drugs were withdrawn at least 8 weeks before the start of the run-in phase.

Study design

Patients who met the inclusion and exclusion criteria started with a placebo run-in period. If the lipid levels were still within the inclusion range after 2 weeks, patients were randomized to treatment with A10 A80 or placebo, administered once daily in the morning. Patients randomized to A80 started with 40 mg for 4 weeks, after which the dose was increased to 80 mg. The total treatment period was 30 weeks. Follow-up visits were scheduled at weeks 4, 10, 20, and 30; during these visits, adverse events were recorded, study medication was counted, blood pressure was measured, and fasting blood samples were collected for safety parameters and lipid profile. There were no changes in concurrent treatment, including hypoglycemic medication, during the study.

Clinical safety and laboratory analysis

At baseline, a medical history was recorded and physical examination was performed. During the follow-up visits, patients were interviewed regarding possible adverse events.

Routine hematology and blood chemistry testing was performed after an overnight fast (12 h) at screening, at randomization, and at the end of the study. All laboratory measurements, except for the safety parameters, were performed at the Lipid Reference Laboratory, Rotterdam, the Netherlands. Standard plasma lipid variables (total cholesterol, HDL cholesterol, triglycerides, free fatty acids [FFAs], and apolipoprotein B [apoB]) were measured at each visit. Total cholesterol and triglyceride levels were measured by enzymatic colorimetric methods (CHOD-PAP and GPO-PAP, Boehringer Mannheim, Mannheim, Germany) on a Hitachi 911 analyzer (Boehringer Mannheim). HDL cholesterol was measured by a direct enzymatic HDL cholesterol method, based on PEG-modified enzymes method (Boehringer Mannheim) on a Hitachi 911 analyzer. LDL cholesterol was estimated by the Friedewald formula (21); apoB was determined on a Hitachi 917 analyzer, using immunoturbidimetric methods (Tina-quant apoB, cat. no.1551779; Boehringer Mannheim). Fasting FFAs were determined using an enzymatic colorimetric method (Wako, NEFA C, cat. no. 994-75409 D). The size of the LDL particles was measured at baseline and at the end of the study by polyacrylamide gradient gel electrophoresis (22). Standardization was achieved by inclusion of LDL samples with known size (donated by Dr. R.M. Krauss). Based on their size, LDL particles were divided into two classes: pattern A reflects the presence of predominantly large, buoyant LDL (>25.5 nm), and pattern B shows the presence of predominantly small, dense LDL particles (<25.5 nm). If both patterns were equally present, patients were classified as pattern AB (23). Lipoprotein lipase (LPL) activity was determined in plasma at baseline and at the end of the study after intravenous injection of heparin (50 IU/kg body wt) using an immunochemical technique. In a sample of 35 healthy subjects (mean age 55.5 years), the LPL activity measured with this technique was 147.4 ± 36.1 units/l (range 89–231).

Safety laboratory tests (creatine kinase, alanine transferase, and aspartate transferase) were performed at all follow-up visits at local laboratories. An increase of the alanine transferase or aspartate transferase levels to >3 times the upper limit of normal or an increase of creatine kinase >10 times the upper limit of normal, verified by repeat testing after 1 week, was considered clinically important and was reported as an adverse event.

Statistics

All data were analyzed by intention to treat. Because patients were randomized, baseline values were not statistically tested between treatment groups. In subjects who did not complete the final visit, the "last observation carried forward" principle was applied. Mean differences between the study groups were analyzed using analysis of covariance, adjusted for baseline levels and study location. Intervention effects were also further adjusted for additional potential confounders, using analysis of covariance. If logarithmic transformation was applied to parameters with skewed distributions, the same results were obtained. Sample size of the study was based to prove a minimal reduction of 0.4 mmol/l in triglyceride levels (compared with placebo) or a difference of 0.4 mmol/l between the two treatment groups (SD 0.8, $\alpha = 0.05$, power 85%). Analyses were performed using SPSS for Windows software (version 9.0; Chicago).

RESULTS

Baseline characteristics

After a screening visit, 251 patients fulfilled the inclusion and exclusion criteria and entered the 2-week placebo run-in period. At baseline, 26 patients had normalized triglyceride levels (<1.5 mmol/l) and 8 patients refused to continue. Finally, 217 patients were randomized. The baseline characteristics of the study population are listed in Table 1. In all three groups, compliance with trial medication

Table 1—*Baseline characteristics of the patients in the DALI study*

	Placebo	Atorvastatin 10 mg	Atorvastatin 80 mg
n	72	73	72
Male sex (%)	46	60	53
Age (years)	58.5 ± 7.5	59.7 ± 7.6	60.1 ± 7.7
Caucasian ethnicity (%)	84	86	82
Duration of diabetes (years)	8.2 ± 5.9	11.1 ± 7.6	12.2 ± 8.3
Diabetes treatment (*n*)			
Diet	2	3	0
Tablets	31	34	30
Insulin	21	19	21
Combination tablets/insulin	18	17	21
Neuropathy (%)	39	32	41
Retinopathy (%)	22	28	37
BMI (kg/m^2)	32.2 ± 6.0	30.0 ± 3.8	30.4 ± 4.5
Waist-to-hip ratio	0.99 ± 0.1	1.00 ± 0.08	1.01 ± 0.1
Treated hypertension (%)	50	49	61
Blood pressure (mmHg)	144 ± 19/85 ± 9	146 ± 17/86 ± 10	145 ± 17/85 ± 9
Present smoking (%)	22	21	17
Fasting glucose (mmol/l)	10.5 ± 3.6	10.5 ± 3.0	10.6 ± 2.9
HbA_{1c} (%)	8.3 ± 1.1	8.3 ± 1.2	8.4 ± 1.1

Data are *n* or mean ± SD.

during the study was >95%. A total of 20 patients (9.2%) did not complete the study because of adverse events ($n = 7$), personal reasons ($n = 10$), protocol violation ($n = 1$), or loss to follow-up ($n = 2$). Personal reasons were defined as reasons not related to the study medication and were mostly due to inability to spend time for participation in the study.

Lipids and lipoproteins

Lipid and lipoprotein plasma values at baseline and after 30 weeks are shown in Table 2. In patients treated with A10, triglyceride levels were significantly lowered by 25% from 2.54 to 1.84 mmol/l ($P < 0.001$). Treatment with A80 resulted in a significant reduction of 35% from 2.85 to 1.78 mmol/l ($P < 0.001$). The difference in decrease of plasma triglyceride levels between the two intervention groups was not statistically significant (Fig. 1).

The effects on triglycerides were also analyzed in two strata of baseline plasma triglyceride levels to investigate whether the baseline levels of plasma triglycerides influenced the lipid-lowering effect of atorvastatin. The first group included all patients with baseline plasma triglyceride levels >2.3 mmol/l ($n = 120$), whereas the second group included 97 patients with baseline plasma triglyceride levels ≤2.3 mmol/l. In both groups, the same results were obtained. In patients with high baseline triglyceride levels, administration of A10 and A80 resulted in a triglyceride reduction of 29.6% and 39.4%, respectively (compared with placebo, both $P < 0.001$; A10 vs. A80, $P > 0.5$). The corresponding figures in patients with low baseline triglyceride levels were 23.4 and 27.9%, respectively (compared with placebo, both $P < 0.001$; A10 vs. A80, $P > 0.4$). Further adjustment for duration of diabetes and BMI did not change the results.

LDL cholesterol was dose-dependently improved to 2.2 mmol/l with administration of A10 (−40.8%, $P < 0.001$) and to 1.7 mmol/l with administration of A80 (−52.3%, $P < 0.001$). The difference between A10 and A80 was statistically significant ($P < 0.001$). Like LDL cholesterol, atorvastatin reduced apoB dose-dependently (Table 2). A10 and A80 increased HDL cholesterol significantly by 5–6%. Consequently, the total-cholesterol/HDL-cholesterol ratio improved, significantly more in patients treated with A80 ($P < 0.005$) (Table 2).

At baseline, relatively few patients had small, dense LDL particles. Patterns A, AB, and B were present in 60.5, 15.3, and 24.2%, respectively, which did not differ between the three intervention groups. There was no overall effect of atorvastatin on the LDL particle size. As a result, the number of patients with dense LDL particles (pattern B) did not differ at the end of the study between the intervention groups: 21.3, 21.4, and 22.2% in the placebo, A10, and A80 groups, respectively. Atorvastatin had no effect on post-heparin LPL activity. Further adjustment for duration of diabetes and BMI did not change the results.

The effects of treatment were compared with target values defined by the American Diabetes Association (24). In both atorvastatin treatment groups, >75% reached the triglyceride treatment

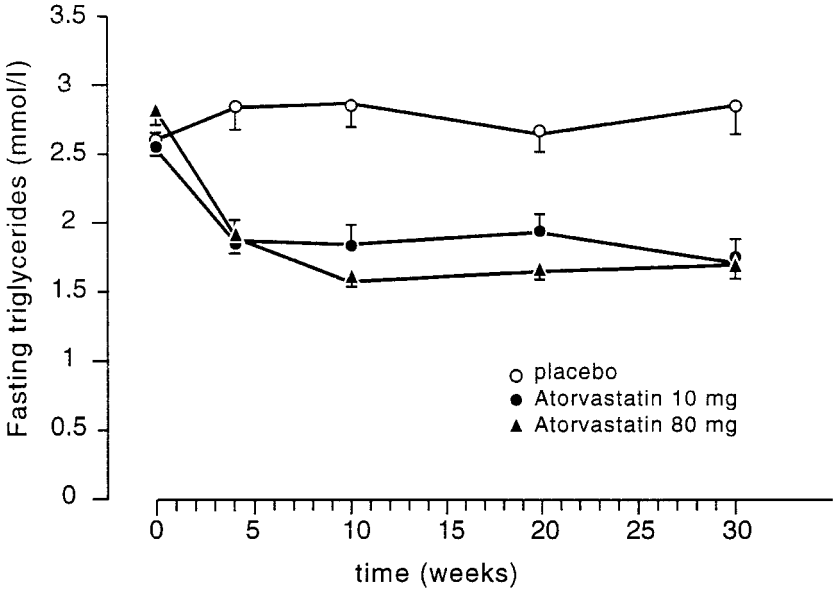

Figure 1—*Triglyceride levels during the DALI study. Values are means ± SEM.*

Table 2—*Lipids and lipoprotein at baseline and end of the DALI study*

	Placebo	Atorvastatin 10 mg	Atorvastatin 80 mg
Triglycerides (mmol/l)			
Baseline	2.62 ± 0.11	2.54 ± 0.10	2.85 ± 0.13
30 weeks	2.88 ± 0.22	1.84 ± 0.10*	1.78 ± 0.16*
Change (%)	10.0 (−1.7 to 21.7)	−25.4 (−31.9 to −18.9)*	−34.6 (−42.7 to −26.5)*
Total cholesterol (mmol/l)			
Baseline	6.0 ± 0.1	5.9 ± 0.1	6.0 ± 0.1
30 weeks	6.0 ± 0.1	4.1 ± 0.1*	3.6 ± 0.1*§
Change (%)	0.5 (−2.0 to 2.0)	−29.8 (−32.4 to −27.2)*	−39.2 (−43.3 to −35.1)*‖
LDL cholesterol (mmol/l)			
Baseline	3.8 ± 0.1	3.7 ± 0.1	3.7 ± 0.1
30 weeks	3.6 ± 0.1	2.2 ± 0.1*	1.7 ± 0.1*§
Change (%)	−2.7 (−7.0 to 1.7)	−40.8 (−43.6 to −37.9)*	−52.3 (−58.9 to −45.7)*§
HDL cholesterol (mmol/l)			
Baseline	1.05 ± 0.02	1.05 ± 0.03	1.03 ± 0.03
30 weeks	1.04 ± 0.03	1.10 ± 0.04	1.09 ± 0.04
Change (%)	−0.9 (−3.7 to 1.9)	6.0 (3.6 to 8.6)†	5.2 (1.8 to 8.6)†
Total cholesterol:HDL cholesterol ratio			
Baseline	5.9 ± 0.2	5.9 ± 0.1	6.1 ± 0.2
30 weeks	6.0 ± 0.1	3.9 ± 0.2*	3.5 ± 0.2*
Change (%)	2.6 (−1.5 to 6.8)	−33.7 (−36.3 to −31.1)*	−42.0 (−46.3 to −37.8)*‖
FFA (mmol/l)			
Baseline	0.67 ± 0.03	0.64 ± 0.03	0.69 ± 0.03
30 weeks	0.72 ± 0.04	0.57 ± 0.03†	0.61 ± 0.03‡
Change (%)	18.6 (2.7 to 34.4)	−5.4 (−14.4 to 3.6)‡	−3.2 (−13.7 to 7.2)‡
apoB (mg/100 ml)			
Baseline	1.27 ± 0.02	1.22 ± 0.02	1.24 ± 0.03
30 weeks	1.25 ± 0.02	0.84 ± 0.02*	0.74 ± 0.03
Change (%)	−1.5 (−4.3 to 1.2)	−30.7 (−33.0 to −28.4)*	−40.2 (−44.2 to −36.1)*§
LDL particle size (nm)			
Baseline	26.0 ± 0.1	26.1 ± 0.1	25.9 ± 0.1
30 weeks	26.0 ± 0.1	26.1 ± 0.1	26.0 ± 0.1
Change (%)	0.3 (−0.3 to 0.9)	−0.03 (−0.5 to 0.5)	0.5 (−0.04 to 1.0)
Lipoprotein lipase (mU/ml)			
Baseline	140.4 ± 5.8	142.6 ± 5.3	138.7 ± 5.3
30 weeks	137.7 ± 6.2	136.1 ± 5.4	133.6 ± 6.2
Change (%)	2.3 (−7.6 to 12.1)	−1.5 (−8.4 to 5.5)	−2.0 (−9.6 to 5.6)

Data are means ± SEM or percent change with the 95% CI. Test for difference among the three groups, adjusted for baseline value and study location: *$P < 0.001$; †$P < 0.005$; ‡$P < 0.05$. Test for difference versus atorvastatin 10 mg, adjusted for baseline value and study location: §$P < 0.001$; ‖$P < 0.005$.

goals (79.5% in A10 and 76.4% in A80, NS). LDL cholesterol treatment goals were reached in 71.2% of the patients treated with A10 and 84.7% of the patients treated with A80, compared with 11.1% in the placebo group. This difference was statistically significant between A10 and A80. HDL cholesterol treatment goals were reached in 35.6% of the A10 group and 44.4% of the patients treated with A80 (NS).

Safety and metabolic control parameters

Adverse events are summarized in Table 3. There was no difference in the number of patients reporting adverse events between the three treatment groups. Twelve serious adverse events were reported. One patient receiving placebo (nonfatal myocardial infarction), one patient treated with A10 (benign neoplasm of skin), and one patient treated with A80 (depressive episode) reported a serious adverse event that was considered "possibly related" to the study drug. The other serious adverse events, not considered related to the study drug, included self-limiting gastroenteritis ($n = 1$) and trauma ($n = 2$) in patients receiving placebo; self-limiting gastroenteritis ($n = 1$), diabetes dysregulation ($n = 1$), and adenocarcinoma of the lung ($n = 1$) in patients using A10; and admission to the hospital for hip replacement surgery ($n = 1$), depressive episode ($n = 1$), and benign neoplasm of the skin ($n = 1$) in patients using A80.

Atorvastatin 80 mg was associated with a slight increase in HbA_{1c} concentration from 8.4 to 8.6% after 30 weeks ($P = 0.06$). In both placebo and A10 groups, a slight decrease in HbA_{1c} was observed after 30 weeks. After 30 weeks, HbA_{1c} in the A80 group differed significantly from either placebo or A10 (both $P < 0.05$). Fasting glucose and blood pressure remained stable during the study in all treatment groups.

Comment

Treatment with atorvastatin 10 and 80 mg resulted in significant reductions in plasma triglyceride and LDL cholesterol

Table 3—*Adverse events and safety parameters in the DAL1 Study*

	Placebo	Atorvastatin 10 mg	Atorvastatin 80 mg
Adverse events			
Gastrointestinal disorder	8 (1)§	11	9 (1)§
Mood disturbances	3 (1)§	1	3
Headache	3	3	3
Heart diseases	3 (1)§	0	2
Respiratory tract disorder	6 (1)§	4	4
Joint disorder/myopathy	9	10	7
Urinary tract disorder	10	13	9
Malaise	6 (1)§	11 (1)§	1
Other	6	19	15
Aspartate transferase (units/l)			
Baseline	24 ± 9	28 ± 12	26 ± 9
30 weeks	25 ± 7	26 ± 8	28 ± 10
Alanine transferase (units/l)			
Baseline	28 ± 11	36 ± 21	33 ± 19
30 weeks	28 ± 11	33 ± 14	37 ± 15
Creatine kinase (units/l)			
Baseline	117 ± 89	121 ± 73	118 ± 64
30 weeks	112 ± 66	126 ± 96	133 ± 96
HbA_{1c} (%)			
Baseline	8.3 ± 1.1	8.3 ± 1.2	8.4 ± 1.1
30 weeks	8.1 ± 1.1	8.0 ± 1.2	8.6 ± 1.3†‡
Fasting glucose (mmol/l)			
Baseline	10.5 ± 3.6	10.5 ± 3.0	10.6 ± 2.9
30 weeks	10.2 ± 2.5	10.3 ± 2.5	11.0 ± 3.2
Blood pressure (mmHg)			
Baseline	144 ± 19/85 ± 9	146 ± 17/86 ± 10	145 ± 17/85 ± 9
30 weeks	144 ± 21/86 ± 11	140 ± 20/84 ± 11	143 ± 16/84 ± 10

Data are *n* or means ± SD. *Test for difference versus baseline, $P < 0.05$; †test for difference among the three groups, $P < 0.05$; ‡test for difference versus atorvastatin 10 mg, $P < 0.005$; §number in bracket indicates withdrawn from the study due to adverse event.

levels and an increase in HDL cholesterol levels in patients with type 2 diabetes. A80 had a significantly greater effect on cholesterol-related variables than A10. The side effects of A10 and A80 did not differ from placebo.

The lower limit of plasma triglyceride levels for inclusion was 1.5 mmol/l. Levels >1.5 mmol/l were associated with an increased risk for cardiovascular disease in diabetic subjects in the Paris Prospective Study and the Bezafibrate Infarction Prevention Registry (14,25). Moreover, 98% of the participants had dyslipidemia, classified according to the American Diabetes Association guidelines (24). The results of the analyses stratified by baseline plasma triglyceride levels indicate that the effects of treatment are independent of baseline plasma triglyceride levels, as is not seen for reduction in plasma LDL cholesterol by statins. Our results show that in patients with type 2 diabetes, high-dose atorvastatin therapy (80 mg) does not have a significant additional effect on reduction of triglycerides compared with a standard dose of 10 mg. The triglyceride-lowering efficacy of atorvastatin in our study is in agreement with previous small studies of administration of 80 mg atorvastatin in nondiabetic patients with primary dyslipidemia (18,19,26). Of the few studies of high doses of other HMG-CoA reductase inhibitors (mainly simvastatin) in patients with diabetes, only one double-blind study was published; that study showed a 15% reduction in triglycerides after administration of simvastatin 40 mg for 24 weeks in 42 patients with type 2 diabetes (20).

The mechanism by which atorvastatin lowers plasma triglyceride levels is not known. Diabetic hypertriglyceridemia is often ascribed to overproduction of VLDL triglycerides as well as impairment of triglyceride clearing due to decreased LPL activity (12,27). In the present study, LPL was in the normal range and was not affected by atorvastatin treatment. Therefore, it is likely that the hepatic triglyceride secretion is affected. Plasma FFAs are the main precursors for hepatic triglyceride synthesis and secretion. Because atorvastatin reduced plasma FFAs, it may be that hepatic triglyceride synthesis and secretion are attenuated.

The decrease in plasma triglycerides and the increase in HDL was not accompanied by an increase in LDL size. It should be noted that LDL size was relatively large. Moreover, based on epidemiological studies, it was found that the presence of small, dense LDL coincides with plasma triglyceride levels >1.6 mmol/l. To obtain a reversal of LDL size toward more buoyant particles, an even lower plasma triglyceride level might be necessary. Micronized fenofibrate has shown to improve LDL size in patients with type 2 diabetes who had higher fasting triglyceride and total cholesterol levels and a predominance (52%) of small, dense LDL at baseline compared with the patients in our study (28).

In the current study, total cholesterol, LDL cholesterol, and apoB levels were significantly reduced in a dose-dependent manner. This reduction is of the same magnitude as that found in studies of atorvastatin in nondiabetic hypercholesterolemic and hypertriglyceridemic patients (18,19). Compared with studies of simvastatin 40 mg in patients with type 2 diabetes, we found a larger reduction in total cholesterol level (39 vs. 30%) and LDL cholesterol level (52 vs. 24–42%) (20,29).

The significant increase from baseline in HDL cholesterol by atorvastatin was consistent with that reported in previous studies. Even small increases in HDL cholesterol may be clinically relevant because they contribute to the reduction of the total cholesterol:HDL cholesterol ratio. This ratio was one of the best predictors of future cardiovascular events in the Framingham study (30). Because treatment with A80 resulted in a significantly lower total cholesterol:HDL cholesterol ratio than A10, the high dose may have an additional protective effect on future cardiovascular events.

The number of serious adverse events and side effects were the same in the three intervention groups. The present study is the first study showing the safety of A80

for a longer treatment period in patients with type 2 diabetes who were using a variety of other medications concomitantly.

Possible limitations of the study are differences at baseline between the placebo and atorvastatin groups. These include BMI and duration of diabetes, which is not likely to influence the results because there is no relation between the duration of diabetes and the metabolism of triglycerides. Because visceral adipocytes are the main source for FFAs supplied to the liver as substrates for triglycerides, the waist-to-hip ratio and FFA levels are more important than BMI (31). Moreover, adjustment for duration of diabetes or BMI did not change the results.

Atorvastatin 80 mg induced a slight increase in HbA_{1c} levels, whereas in patients using A10 and placebo, the HbA_{1c} level decreased slightly. Other studies have shown inconsistent results of lipid-lowering therapy on glycemic control in patients with diabetes, and several clinical studies reported an increase in HbA_{1c} level with either fluvastatin or simvastatin (20,32–34).

CONCLUSIONS — In conclusion, administration of atorvastatin at doses of either 10 or 80 mg is effective in the treatment of diabetic dyslipidemia (elevated triglyceride, normal to elevated LDL cholesterol, low HDL cholesterol) in patients with type 2 diabetes. Both doses were well tolerated in our patient population.

APPENDIX

Members of the DALI Study Group

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References

1. de Vegt F, Dekker JM, Stehouwer CD, Nijpels G, Bouter LM, Heine RJ: Similar 9-year mortality risks and reproducibility for the World Health Organization and American Diabetes Association glucose tolerance categories: the Hoorn Study. *Diabetes Care* 23:40–44, 2000
2. Stamler J, Vaccaro O, Neaton JD, Wentworth D: Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. *Diabetes Care* 16:434–444, 1993
3. Uusitupa MI, Niskanen LK, Siitonen O, Voutilainen E, Pyorala K: Ten-year cardiovascular mortality in relation to risk factors and abnormalities in lipoprotein composition in type 2 (non-insulin-dependent) diabetic and non-diabetic subjects. *Diabetologia* 36:1175–1184, 1993
4. de Grauw WJ, van de Lisdonk EH, van den Hoogen HJ, Van Weel C: Cardiovascular morbidity and mortality in type 2 diabetic patients: a 22-year historical cohort study in Dutch general practice. *Diabet Med* 12:117–122, 1995
5. Manson JE, Colditz GA, Stampfer MJ, Willett WC, Krolewski AS, Rosner B, Arky RA, Speizer FE, Hennekens CH: A prospective study of maturity-onset diabetes mellitus and risk of coronary heart disease and stroke in women. *Arch Intern Med* 151:1141–1147, 1991
6. U.K. Prospective Diabetes Study (UKPDS) Group: Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 352:837–853, 1998
7. Pyorala K, Pedersen TR, Kjekshus J, Faergeman O, Olsson AG, Thorgeirsson G: Cholesterol lowering with simvastatin improves prognosis of diabetic patients with coronary heart disease: a subgroup analysis of the Scandinavian Simvastatin Survival Study (4S). *Diabetes Care* 20:614–620, 1997
8. Goldberg RB, Mellies MJ, Sacks FM, Moye LA, Howard BV, Howard WJ, Davis BR, Cole TG, Pfeffer MA, Braunwald E: Cardiovascular events and their reduction with pravastatin in diabetic and glucose-intolerant myocardial infarction survivors with average cholesterol levels: subgroup analyses in the cholesterol and recurrent events (CARE) trial: the Care Investigators. *Circulation* 98:2513–2519, 1998
9. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group: Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med* 339:1349–1357, 1998
10. Downs JR, Clearfield M, Weis S, Whitney E, Shapiro DR, Beere PA, Langendorfer A, Stein EA, Kruyer W, Gotto AM Jr: Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. *JAMA* 279:1615–1622, 1998
11. West of Scotland Coronary Prevention Study Group: Identification of high-risk groups and comparison with other cardiovascular intervention trials. *Lancet* 348:1339–1342, 1996
12. Haffner SM: Management of dyslipidemia in adults with diabetes. *Diabetes Care* 21:160–178, 1998
13. Hokanson JE, Austin MA: Plasma triglyceride level is a risk factor for cardiovascular disease independent of high-density lipoprotein cholesterol level: a meta-analysis of population-based prospective studies. *J Cardiovasc Risk* 3:213–219, 1996
14. Fontbonne A, Eschwege E, Cambien F, Richard JL, Ducimetiere P, Thibult N, Warnet JM, Claude JR, Rosselin GE: Hypertriglyceridaemia as a risk factor of coronary heart disease mortality in subjects with impaired glucose tolerance or diabetes: results from the 11-year follow-up of the Paris Prospective Study. *Diabetologia* 32:300–304, 1989
15. Assmann G, Schulte H: Relation of high-density lipoprotein cholesterol and triglycerides to incidence of atherosclerotic coronary artery disease (the PROCAM experience): Prospective Cardiovascular Munster Study. *Am J Cardiol* 70:733–737, 1992
16. Tenkanen L, Pietila K, Manninen V, Manttari M: The triglyceride issue revisited: findings from the Helsinki Heart Study. *Arch Intern Med* 154:2714–2720, 1994
17. Castelli WP: The triglyceride issue: a view from Framingham. *Am Heart J* 112:432–437, 1986
18. Jones P, Kafonek S, Laurora I, Hunninghake D: Comparative dose efficacy study

of atorvastatin versus simvastatin, pravastatin, lovastatin, and fluvastatin in patients with hypercholesterolemia (the CURVES study). *Am J Cardiol* 81:582–587, 1998
19. Bakker-Arkema RG, Davidson MH, Goldstein RJ, Davignon J, Isaacsohn JL, Weiss SR, Keilson LM, Brown WV, Miller VT, Shurzinske LJ, Black DM: Efficacy and safety of a new HMG-CoA reductase inhibitor, atorvastatin, in patients with hypertriglyceridemia. *JAMA* 275:128–133, 1996
20. Tikkanen MJ, Laakso M, Ilmonen M, Helve E, Kaarsalo E, Kilkki E, Saltevo J: Treatment of hypercholesterolemia and combined hyperlipidemia with simvastatin and gemfibrozil in patients with NIDDM: a multicenter comparison study. *Diabetes Care* 21:477–481, 1998
21. Friedewald WT, Levy RI, Fredrickson DS: Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem* 18:499–502, 1972
22. Hoogerbrugge N, Jansen H: Atorvastatin increases low-density lipoprotein size and enhances high-density lipoprotein cholesterol concentration in male, but not in female patients with familial hypercholesterolemia. *Atherosclerosis* 146:167–174, 1999
23. Reaven GM, Chen YD, Jeppesen J, Maheux P, Krauss RM: Insulin resistance and hyperinsulinemia in individuals with small, dense low density lipoprotein particles. *J Clin Invest* 92:141–146, 1993
24. American Diabetes Association: Management of dyslipidemia in adults with diabetes. *Diabetes Care* 21:179–182, 1998
25. Haim M, Benderly M, Brunner D, Behar S, Graff E, Reicher-Reiss H, Goldbourt U: Elevated serum triglyceride levels and long-term mortality in patients with coronary heart disease: the Bezafibrate Infarction Prevention (BIP) Registry. *Circulation* 100:475–482, 1999
26. Stein EA, Lane M, Laskarzewski P: Comparison of statins in hypertriglyceridemia. *Am J Cardiol* 81:66B–69B, 1998
27. Ginsberg HN: Lipoprotein physiology in nondiabetic and diabetic states: relationship to atherogenesis. *Diabetes Care* 14: 839–855, 1991
28. Feher MD, Caslake M, Foxton J, Cox A, Packard CJ: Atherogenic lipoprotein phenotype in type 2 diabetes: reversal with micronised fenofibrate. *Diabetes Metab Res Rev* 15:395–399, 1999
29. Cassader M, Ruiu G, Gambino R, Alemanno N, Veglia F, Pagano G: Hypercholesterolemia in non-insulin-dependent diabetes mellitus: different effect of simvastatin on VLDL and LDL cholesterol levels. *Atherosclerosis* 99:47–53, 1993
30. Castelli WP: Cholesterol and lipids in the risk of coronary artery disease: the Framingham Heart Study. *Can J Cardiol* 4 (Suppl. A):5A–10A, 1988
31. Bjorntorp P: Metabolic implications of body fat distribution. *Diabetes Care* 14: 1132–1143, 1991
32. Hwu CM, Kwok CF, Chen HS, Shih KC, Lee SH, Hsiao LC, Lin SH, Ho LT: Lack of effect of simvastatin on insulin sensitivity in type 2 diabetic patients with hypercholesterolaemia: results from a double-blind, randomized, placebo-controlled crossover study. *Diabet Med* 16:749–754, 1999
33. Jokubaitis LA, Knopp RH, Frohlich J: Efficacy and safety of fluvastatin in hyperlipidaemic patients with non-insulin-dependent diabetes mellitus. *J Intern Med Suppl* 736:103–107, 1994
34. Knopp RH, Frohlich J, Jokubaitis LA, Dawson K, Broyles FE, Gomez-Coronado D: Efficacy and safety of fluvastatin in patients with non-insulin-dependent diabetes mellitus and hyperlipidemia. *Am J Med* 96:69S–78S, 1994