Metabolic Effects of Fluvastatin Extended Release 80 mg and Atorvastatin 20 mg in Patients with Type 2 Diabetes Mellitus and Low Serum High-Density Lipoprotein Cholesterol Levels: A 4-Month, Prospective, Open-Label, Randomized, Blinded-End Point (Probe) Trial

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ABSTRACT

Background: Diabetic dyslipidemia is characterized by greater triglyceridation of all lipoproteins and low levels of plasma high-density lipoprotein cholesterol (HDL-C). In this condition, the serum level of low-density lipoprotein cholesterol (LDL-C) is only slightly elevated. The central role of decreased serum HDL-C level in diabetic cardiovascular disease has prompted the establishment of a target of ≥ 50 mg/dL in patients with diabetes mellitus (DM).

Objective: The aim of the study was to assess the effects of once-daily administration of fluvastatin extended release (XL) 80 mg or atorvastatin 20 mg on serum HDL-C levels in patients with type 2 DM and low levels of serum HDL-C.

Methods: This 4-month, prospective, open-label, randomized, blinded-end point (PROBE) trial was conducted at Endocrinology and Diabetology Service, L. Sacco-Polo University Hospital (Milan, Italy). Patients aged 45 to 71 years with type 2 DM receiving standard oral antidiabetic therapy, with serum HDL-C levels < 50 mg/dL, and with moderately high serum levels of LDL-C and triglycerides (TG) were enrolled. After 1 month of lifestyle modification and dietary intervention, patients who were still showing a decreased HDL-C level were randomized, using a 1:1 ratio, to receive fluvastatin XL 80-mg tablets or atorvastatin 20-mg tablets, for 3 months. Lipoprotein metabolism was assessed by measuring serum levels of LDL-C, HDL-C, TG, apolipoprotein (apo) A-I (the lipoprotein that carries HDL), and apo B (the lipoprotein that binds very low-density lipoprotein cholesterol, intermediate-density lipoprotein, and LDL on a molar basis). Patients were assessed every 2 weeks for treatment com-

pliance and subjective adverse events. Serum creatine phosphokinase and liver enzymes were assessed before the run-in period, at the start of the trial, and at 1 and 3 months during the study.

Results: One hundred patients were enrolled (50 patients per treatment group; fluvastatin XL group: 33 men, 17 women; mean [SD] age, 58 [12] years; atorvastatin group: 39 men, 11 women; mean [SD] age, 59 [11] years). In the fluvastatin group after 3 months of treatment, mean (SD) LDL-C decreased from 149 (33) to 95 (25) mg/dL (36%; $P < 0.01$), TG decreased from 437 (287) to 261 (164) mg/dL (40%; $P < 0.01$), and HDL-C increased from 41 (7) to 46 (10) mg/dL (12%; $P < 0.05$). In addition, apo A-I increased from 118 (18) to 124 (15) mg/dL (5%; $P < 0.05$) and apo B decreased from 139 (27) to 97 (19) mg/dL (30%; $P < 0.05$). In the atorvastatin group, LDL-C decreased from 141 (25) to 84 (23) mg/dL (40%; $P < 0.01$) and TG decreased from 411 (271) to 221 (87) mg/dL (46%; $P < 0.01$). Neither HDL-C (41 [7] vs 40 [6] mg/dL; 2%) nor apo A-I (117 [19] vs 114 [19] mg/dL; 3%) changed significantly. However, apo B decreased significantly, from 131 (20) to 92 (17) mg/dL (30%; $P < 0.05$). Mean changes in HDL-C (+5 [8] vs -1 [2] mg/dL; $P < 0.01$) and apo A-I (+6 [18] mg/dL vs -3 [21] mg/dL; $P < 0.01$) were significantly greater in the fluvastatin group than in the atorvastatin group, respectively. However, the decreases in LDL-C (54 [31] vs 57 [32] mg/dL), TG (177 [219] vs 190 [65] mg/dL), and apo B (42 [26] vs 39 [14] mg/dL) were not significantly different between the fluvastatin and atorvastatin groups, respectively. No severe adverse events were reported.

Conclusions: Fluvastatin XL 80 mg and atorvastatin 20 mg achieved mean serum LDL-C (≤ 100 mg/dL) and apo B target levels (≤ 100 mg/dL) in the majority of this population of patients with type 2 DM, but mean serum HDL-C level was increased significantly only with fluvastatin—16 patients (32%) in the fluvastatin group compared with none in the atorvastatin group achieved HDL-C levels ≥ 50 mg/dL. The increase in HDL-C in the fluvastatin-treated patients was associated with an increase in apo A-I, suggesting a potential pleiotropic and selective effect in patients with low HDL-C levels. (*Curr Ther Res Clin Exp.* 2004; 65:330–344) Copyright © 2004 Excerpta Medica, Inc.

Key words: fluvastatin XL, atorvastatin, type 2 DM, HDL, LDL, triglycerides, apo A-I, apo B.

INTRODUCTION

Diabetic dyslipidemia is probably the main cause of cardiovascular mortality in diabetes mellitus (DM).^{1–32} This condition is characterized by an increase in the very low-density lipoprotein-mediated triglyceridation of all classes of lipoproteins, which, after extensive de novo delipidation by hepatic and possibly endothelial lipase, generate small, dense low-density lipoprotein (sdLDL) and small, dense high-density lipoprotein (sdHDL). sdLDL is highly atherogenic because of its ability to cross the endothelium and enter the vascular smooth

muscle layer, whereas the accelerated clearance of sdHDL ultimately decreases HDL cholesterol (HDL-C) levels and increases the renal excretion of apolipoprotein (apo) A-I.^{3,7,11} HDL-C protects against atherosclerosis because it has an antioxidant effect on LDL, as well as other potentially beneficial properties,^{3,28–32} and apo A-I is protective insofar as it is mainly responsible for reversing cholesterol efflux (from the endothelium to the liver). Therefore, it is clear that any drug aimed at controlling diabetic dyslipidemia should decrease cholesterol (mainly the sdLDL subfraction) and increase HDL-C and apo A-I.

Post hoc analyses of the Scandinavian Simvastatin Survival Study (4S),^{33,34} the Cholesterol And Recurrent Events (CARE) study,³⁵ and the Long-Term Treatment with Pravastatin in Ischemic Disease (LIPID) study³⁶ suggested that treatment with simvastatin or pravastatin may lead to a better outcome in patients with DM than in patients without it. However, there is a paucity of large-scale, prospective, randomized trials designed for patients with DM.³⁷ The Diabetes Atherosclerosis Intervention Study (DAIS)³⁸ showed that fenofibrate reduced the increase in coronary stenosis by 42% (although the final mortality/morbidity data have not yet been published), and the Heart Protection Study (HPS)³⁹ showed that simvastatin decreased all-cause mortality in patients with DM. In the Lescol Intervention Prevention Study (LIPS),⁴⁰ fluvastatin-treated patients with DM undergoing percutaneous intervention experienced fewer major cardiac events. The Veterans Affairs HDL Intervention Trial (VA-HIT)⁴¹ reported a decrease in cardiovascular events in 627 patients with DM and low HDL-C levels who experienced a myocardial infarction when treated with gemfibrozil.⁴² However, a subgroup analysis revealed that the improvement in cardiovascular morbidity was unrelated to the HDL-C-enhancing effect of gemfibrozil, thereby casting some doubt on the clinical relevance of low target HDL-C levels in patients with DM.^{41,43–45} The Collaborative Atorvastatin Diabetes Study^{46,47} (CARDS) was halted early because the study demonstrated that atorvastatin 10 mg decreased major cardiovascular and surgical events in patients with DM.

We are still awaiting the final clinical outcomes^{37,47} of the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, and the Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non Insulin Dependent Diabetes Mellitus (ASPEN) study, which may provide the definitive prospective data needed for better patient management. The characteristics of the ACCORD and ASPEN studies have been described elsewhere.^{19,37}

Previous studies of type 2 DM have shown that fluvastatin extended-release (XL) 80 mg decreased sdLDL (especially in patients with more extensive lipoprotein triglyceridation), although the results were accompanied by a small, nonsignificant increase in HDL.⁴⁸ This clinically meaningful study was placebo controlled and had an active treatment period of 8 weeks; the patients were not selected on the basis of their HDL-C level.

Atorvastatin, a potent hydroxymethylglutaryl coenzyme A inhibitor that has been widely used to manage mixed dyslipidemia in patients with DM, potently decreases LDL cholesterol (LDL-C) and improves the levels of sdLDL. Its effect on HDL-C is biphasic; increasing the dosage to >20 mg/d usually leads to a decrease in HDL-C level,⁴⁹ possibly because of a disproportionate increase in HDL clearance compared with HDL production.

Therefore, we performed this prospective, randomized, clinical trial comparing fluvastatin XL 80 mg and atorvastatin 20 mg to verify whether these drugs are capable of increasing HDL-C to ≥ 50 mg/dL in patients with type 2 DM and low HDL-C levels.

PATIENTS AND METHODS

Study Design

This 4-month prospective, open-label, randomized, blinded-end point (PROBE) study (including a 4-week dietary run-in period) was conducted at the Endocrinology and Diabetology Service, L. Sacco-Polo University Hospital (Milan, Italy). The study protocol was approved by the hospital's ethics committee.

Patients

Caucasian male and postmenopausal female patients aged 45 to 71 years with type 2 DM, mixed dyslipidemia (LDL-C, 150–300 mg/dL; triglycerides [TG], >200 mg/dL), and HDL-C <50 mg/dL after 4 weeks on a National Cholesterol Education Panel⁵⁰ step I or II diet were eligible for the study. Type 2 DM had to have been diagnosed ≥ 12 weeks before the dietary run-in period. The exclusion criteria were surgery, myocardial infarction, or angioplasty during the 6 months preceding randomization; poorly controlled hypertension (blood pressure >160/>100 mm Hg); hepatic disease; chronic renal failure; myopathy; alcohol/drug abuse; known hypersensitivity to statins; pregnancy or breastfeeding; lipid-lowering therapy within the 8 weeks preceding the study; and the use of oral contraceptives at the start of the study. All eligible patients provided written informed consent to participate.

Angiotensin-converting enzyme (ACE) inhibitors, hydrochlorothiazide, angiotensin-receptor antagonists, and allopurinol were allowed during the study. No other medications, including nonsteroidal anti-inflammatory drugs, vitamins, and other supplements, were allowed.

Methods

Medical history was taken and physical examination was performed at screening at our outpatient facilities for DM (6–12 months previous to the run-in period). Medical history and physical examination were replicated during the visits before run-in and during the trial (visits were done every 2 weeks). Also during these visits, body weight was measured and body mass index (BMI) was

calculated. Glycosylated hemoglobin (HbA_{1c}), serum creatine phosphokinase (CPK), liver enzymes, and blood pressure were measured. DM was considered in good control if HbA_{1c} was $\leq 7\%$ and in relatively good control if it was $< 8\%$. We did include patients with $\text{HbA}_{1c} \leq 8\%$. Heart rate was measured throughout the study. Blood pressure was measured throughout the study by the same 2 persons (M.B. and E.C.) in the left arm each time while the patient was in the sitting position. The mean of 3 measurements was used for analysis. Tolerability (adverse events) was assessed using patient interview and routine biochemical measurements (CPK, liver enzymes, and complete blood count) every 2 weeks during the run-in and the trial.

After the 4-week dietary run-in period and blood lipid evaluation, patients with a low HDL-C level (< 50 mg/dL) and a mildly to moderately elevated LDL-C and TG were assigned, in a 1:1 ratio based on a randomization list, to fluvastatin XL 80-mg tablets or atorvastatin 20-mg tablets at bedtime for 12 weeks. Thus, only patients satisfying the biochemical indication of HDL-C < 50 mg/dL and diabetic dyslipidemia underwent randomization. The PROBE methodology^{51–53} consists of a prospective, open-label trial in which neither patients nor investigators are blinded to treatment group, but the final end points are analyzed by a blinded observer. Interim lipid levels were not revealed to the investigators or patients. The antidiabetic and antihypertensive pharmacologic treatments were left unchanged throughout the trial. Patients were followed up by an experienced dietitian throughout the study (including run-in phase) to monitor diet and exercise. The primary end point of the study was the change in HDL-C and apo A-I levels from baseline (the end of the 1-month period of dietary advice and lifestyle changes) to the end of the 3-month active treatment period.

Laboratory Procedures

Before study entry (week –4), after the dietary run-in period (baseline), and after 12 weeks of active treatment, 12-hour fasting venous blood samples by one of the investigators (E.C.) were aliquoted for serum and EDTA-plasma and centrifuged at 3000 rpm at 4°C for 20 minutes. Serum was used immediately to measure CPK and liver enzymes, and EDTA-plasma was used immediately to measure HbA_{1c} . Serum was stored at 4°C for ≤ 1 week, and assayed for lipid biochemistry.

Serum levels of total cholesterol, HDL-C, and TG were determined enzymatically using the cholesterol oxidase-peroxidase aminophenazone phenol and the glycerol-3-phosphate oxidase-peroxidase aminophenazone phenol methods (Roche Diagnostics, Mannheim, Germany). Serum LDL-C level was calculated using the Friedewald equation,⁵⁴ or, in patients with high TG levels, it was directly assayed after agarose gel electrophoresis and enzymatic cholesterol staining.⁵⁵ Serum apo levels were determined by means of turbidimetry using specific polyclonal antisera (Rolf Greiner Biochemica, Flacht, Germany).

Statistical Analysis

The changes in serum lipid levels between baseline and 12 weeks and between treatments were compared using the unpaired Student *t* test or the Mann-Whitney *U* test, as appropriate. Within-group tests for significance of change from baseline were performed using the paired Student *t* test. Bivariate correlations were analyzed using Pearson's correlation coefficients. $P \leq 0.05$ was considered statistically significant. Statistical analysis was performed using GraphPad Prism version 4 (GraphPad Software, Inc., San Diego, California).

RESULTS

One hundred patients were enrolled (fluvastatin XL group: 33 men, 17 women; mean [SD] age, 58 [12] years; atorvastatin group: 39 men, 11 women; mean [SD] age, 59 [11] years) (**Table I**). At baseline, most patients were being treated with metformin (fluvastatin group, 45 patients [90%]; atorvastatin group, 44 [88%]); the other antidiabetic drugs being used were glimepiride 2 to 8 mg/d, glibenclamide ≤ 7.5 mg TID, and insulin glargine (**Table I**). In most cases (81%), metformin was started ≥ 12 weeks before study entry, and minor changes in body weight and BMI were observed 8 to 10 weeks before the start of the study. Control of DM (if we assume that good control is $\text{HbA}_{1c} \leq 7\%$ and that relatively good control is $\leq 8\%$) was shown by the mean (SD) HbA_{1c} level of 7.4% (1.2%) in the fluvastatin group and 7.3% (1.7%) in the atorvastatin group. There was no difference in diet or exercise between the groups before or after study entry.

At baseline and throughout the study, 40 (80%) of the patients in the fluvastatin group (mean [SD] systolic blood pressure [SBP], 148 [10] mm Hg; mean

Table I. Baseline demographic and clinical characteristics of the study patients (N = 100).*

Characteristic	Fluvastatin (n = 50)	Atorvastatin (n = 50)
Age at recruitment, y, mean (SD)	58 (12)	59 (11)
Sex, no. (%)		
Men	33 (66)	39 (78)
Women	17 (34)	11 (22)
Diabetes duration, mean (SD), y	6 (4)	7 (3)
Diabetes therapy, no. (%)		
Metformin	45 (90)	44 (88)
Glimepiride	22 (44)	23 (46)
Glibenclamide	12 (24)	11 (22)
Insulin glargine	14 (28)	13 (26)

*No significant between-group differences were found.

[SD] diastolic blood pressure [DBP], 95 [7] mm Hg) and 39 (78%) in the atorvastatin group (mean [SD] SBP, 147 [12] mm Hg; mean [SD] DBP, 93 [4] mm Hg) were hypertensive and were being treated with ACE inhibitors; 10 patients (20%) in both groups were also receiving low-dose hydrochlorothiazide. The remaining 2 patients (4%) in the fluvastatin group were being treated with angiotensin receptor antagonists. Twenty patients (fluvastatin group, 11 patients [22%]; atorvastatin group, 9 patients [18%]) were receiving allopurinol (300 mg/d).

Two patients (4%; 1 man and 1 woman) in the fluvastatin group were withdrawn in the first week of treatment due to dyspepsia, and 3 patients in the atorvastatin group were withdrawn within the first 4 weeks of treatment (1 woman due to dyspepsia and 2 men due to muscle ache without elevations in CPK activity). All patients who were withdrawn were replaced by 5 consecutive patients who underwent the same run-in period and who were admitted on the basis of the same biochemical criteria. Final results include the findings obtained in patients who completed the trial.

Sixteen patients (32%) in the fluvastatin group achieved HDL-C levels of ≥ 50 mg/dL after 12 weeks compared with none of the patients in the atorvastatin group. Both treatments were well tolerated, and no significant changes in serum CPK or liver enzyme activities were observed. No major adverse events were found.

The effects of fluvastatin XL and atorvastatin on plasma lipid and apo levels are shown in **Table II** and the **figure**. In the fluvastatin group after 12 weeks of treatment, mean (SD) LDL-C decreased from 149 (33) to 95 (25) mg/dL (36%; $P < 0.01$), mean (SD) TG decreased from 437 (287) to 261 (164) mg/dL (40%; $P < 0.01$), and mean (SD) HDL-C increased from 41 (7) to 46 (10) mg/dL (12%; $P < 0.05$). Furthermore, mean (SD) apo A-I increased from 118 (18) to 124 (15) mg/dL (5%; $P < 0.05$), and mean (SD) apo B decreased from 139 (27) to 97 (19) mg/dL (30%; $P < 0.05$).

In the atorvastatin group, mean (SD) LDL-C decreased from 141 (25) to 84 (23) mg/dL (change, 40%; $P < 0.01$), and mean (SD) TG from 411 (271) to 221 (87) mg/dL (change, 46%; $P < 0.01$). Neither mean (SD) HDL-C (41 [7] vs 40 [6]; change, 2%) nor mean (SD) apo A-I (117 [19] vs 114 [19] mg/dL; change, 3%) changed significantly. However, mean (SD) apo B decreased significantly, from 131 (20) to 92 (17) mg/dL (change, 30%; $P < 0.05$).

Mean (SD) changes in HDL-C (5 [8] vs -1 [2] mg/dL; $P < 0.01$) and apo A-I (6 [18] vs -3 [21] mg/dL; $P < 0.01$) were significantly greater in the fluvastatin group than in the atorvastatin group, respectively. However, the decreases in LDL-C (54 [31] vs 57 [32] mg/dL), TG (176 [219] vs 190 [65] mg/dL), and apo B (42 [26] vs 39 [14] mg/dL) were not significantly different between treatment groups.

DISCUSSION

The main findings in this study are the increases in serum HDL-C and apo A-I levels in patients with DM admitted to the study on the basis of low HDL-C

Table II. Mean (SD) serum lipid and apolipoprotein (apo) levels (mg/dL) at baseline and after 3 months of active treatment.

Variable	Fluvastatin (n = 50)				Atorvastatin (n = 50)			
	Baseline	Month 3	Δ	$\Delta\%$	Baseline	Month 3	Δ	$\Delta\%$
LDL-C	149 (33)	95 (25)	-54 (31)	-36*	141 (25)	84 (23)	-57 (32)	-40*
TG	437 (287)	261 (164)	-176 (219)	-40*	411 (271)	221 (87)	-190 (65)	-46*
HDL-C	41 (7)	46 (10)	+5 (8) [†]	+12 [‡]	41 (7)	40 (6)	-1 (2)	-2
apo A-I	118 (18)	124 (15)	+6 (18) [†]	+5 [‡]	117 (19)	114 (19)	-3 (21)	-3
apo B	139 (27)	97 (19)	-42 (26)	-30 [‡]	131 (20)	92 (17)	-39 (14)	-30 [‡]

LDL-C = low-density lipoprotein cholesterol; TG = triglycerides; HDL-C = high-density lipoprotein cholesterol.

* $P < 0.01$ versus baseline.[†] $P < 0.01$ versus atorvastatin.[‡] $P < 0.05$ versus baseline.

Figure. Mean percentage changes in serum levels of high-density lipoprotein cholesterol (HDL-C) and apolipoprotein (apo) A-I after 3 months of treatment with fluvastatin extended release (XL) 80 mg and atorvastatin 20 mg. * $P < 0.01$ versus atorvastatin.

levels (<50 mg/dL) and diabetic dyslipidemia, after a run-in period of dietary advice of 1 month, and subsequently randomized to receive fluvastatin XL 80 mg or atorvastatin 20 mg for 3 months.

We previously reported similar results in ischemic patients.⁵⁶ Olsson et al⁵⁷ found that fluvastatin XL increased HDL-C by 14.5% and decreased TG by 21.8% in patients with mixed dyslipidemia (but not DM). These findings are very similar to the findings in the present study of patients with DM and mixed dyslipidemia. Interestingly, Foldes et al⁵⁸ found that fluvastatin 20 mg increased HDL-C by ~35% in patients with DM who had undergone successful kidney transplantation and showed no signs of renal failure, whereas Lintott et al⁵⁹ observed no change in HDL-C levels in nondiabetic patients with chronic renal insufficiency. Tomlinson et al⁶⁰ reported an increase in HDL-C of ~10% and an increase in apo A-I of ~7% in a group of Chinese patients that included patients with type 2 DM, and Ballantyne et al⁶¹ observed an increase in HDL-C of ~16% in patients with coronary artery disease, without DM, and with low HDL-C levels that was larger than that achieved in patients with normal HDL-C levels (>35 mg/dL). One study⁶² has shown that fluvastatin 20 to 40 mg/d increases HDL-C in diabetic patients; in this study, patients were treated with fluvastatin 20 mg for 6 weeks, followed by 20 mg BID for an additional 6 weeks; HDL-C increased by 4.6% by weeks 9 to 12.

Our results with fluvastatin are different from those observed with atorvastatin, which did not increase HDL-C levels in our population of patients with DM and low HDL-C levels. Van Venrooij et al⁶³ found that atorvastatin increased HDL-C (by 7.2%) only in a subgroup of patients with type 2 DM who had a

mutation in cholesteryl ester transfer protein (CETP) B1B1 and the lowest baseline HDL-C levels, but not in patients with DM and higher HDL-C levels.

The increase in serum HDL-C levels found with fluvastatin use in this and other studies^{57–59} does not seem to be related to the changes in other lipid parameters.

The significant increase in HDL-C and apo A-I found with fluvastatin XL use in our study does not seem to fit with the data of Winkler et al,⁴⁸ who reported a significant decrease in sdLDL only in patients with DM and the mixed dyslipidemia phenotype, but no apparent increase in HDL-C or apo A-I. However, careful analysis of the data relating to this multicenter clinical trial shows that, by chance, the patients with very low HDL-C levels were all included in the placebo arm and the patients with higher HDL-C levels were included in the fluvastatin XL 80-mg arm. As shown by our data and those of others,^{57–59} it is possible that increases in HDL are greater in patients with low baseline HDL-C levels, and that Winkler et al⁴⁸ missed the increase in HDL-C because of an involuntary selection bias.

The decreased HDL-C level in patients with DM and mixed dyslipidemia seems to be related to the increased triglyceridation of HDL-C, which, after undergoing hepatic lipase enzymatic activity, is extensively delipidated to sdHDL-C that is rapidly cleared by the kidney.^{2,3,7,9,11,47} The same mechanisms also generate sdLDL.^{2,3,7,9,11,47} Fluvastatin has consistently been found to selectively decrease sdLDL (LDL-5 and LDL-6) and to increase large, buoyant HDL2 (a subspecies of HDL) in nondiabetic patients with mixed dyslipidemia.⁶⁴ This effect was not related to the inhibition of CETP⁶⁴ but is possibly related to an inhibitory effect of fluvastatin on hepatic lipase.⁶² On the other hand, fluvastatin has been shown to directly affect the enzymatic activity of phospholipase A2^{65,66} and phospholipase D,⁶⁷ 2 enzymes that may decrease HDL-C levels by promoting oxidative processes.⁶⁸

The increase in HDL-C induced by fluvastatin is a consistent finding in patients with DM (who typically have high levels of hepatic lipase activity^{2,3,7,11}), as well as in patients with mixed familial dyslipidemia who also have high levels of hepatic lipase activity.^{2,3,69,70} Therefore, it is tempting to speculate that the effect of fluvastatin on HDL-C levels in patients with type 2 DM or those with mixed familial combined dyslipidemia and low levels of HDL-C is associated with a particular action of the drug on hepatic lipase. This could be the simplest explanation for its effect on HDL-C and sdLDL, although other explanations based on the effect of fluvastatin on the transfer of lipids among lipoproteins are possible.^{28,63,69,71–74}

CONCLUSIONS

Both fluvastatin XL 80 mg and atorvastatin 20 mg achieved target mean serum levels of LDL-C (≤ 100 mg/dL) and apo B (≤ 100 mg/dL) in the majority of patients with type 2 DM in this study. However, only fluvastatin significantly

increased mean HDL-C—16 patients (32%) in the fluvastatin group achieved HDL-C levels of ≥ 50 mg/dL after 3 months of treatment compared with none in the atorvastatin group. The increase in HDL-C in the fluvastatin-treated patients was associated with an increase in apo A-I, suggesting a possible pleiotropic effect in patients with low serum HDL-C levels.

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