DOI: 10.1111/j.1365-2362.2009.02126.x

ORIGINAL ARTICLE

Fluvastatin/fenofibrate vs. simvastatin/ezetimibe in patients with metabolic syndrome: different effects on LDL-profiles

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ABSTRACT

Background Patients with metabolic syndrome (MS) and type 2 diabetes (T2DM) show increased risk for coronary artery disease. Lipoprotein metabolism is characterized by elevated triglycerides (TG), low high-density lipoprotein cholesterol (HDL-C) and predominance of atherogenic small, dense low-density lipoprotein (sdLDL), while low-density lipoprotein (LDL) cholesterol is only slightly elevated.

Methods Multicentre, randomized, open-label cross-over study investigating the effect of combination of fluvastatin/fenofibrate (80/200 mg) (F&F) on LDL-subfractions compared with combination of simvastatin/ezetimibe (20/10 mg) (S&E) in patients with MS/T2DM.

Results Seventy-five patients were randomized, 69 completed the study and LDL-subfractions of 56 patients were analysed. Thirty-eight out of 56 patients (68%) showed a profile dominated by sdLDL. In these, TG and total cholesterol (TC) were elevated compared with non-sdLDL patients. In all patients, reduction of TC and LDL cholesterol (LDL-C) by S&E was stronger than by F&F. The increase of HDL-C was stronger with S&E in the non-sdLDL group, whereas in the sdLDL group, there was no difference between treatments. In non-sdLDL patients, there was no effect on TG or LDL-radius. However, in the sdLDL group, F&F was more effective in reducing TG and increased LDL radius, whereas S&E reduced LDL radius even further.

Conclusions S&E is more efficient in reducing TC and LDL-C. This is also true for HDL-C increase in non-sdLDL patients. However, in patients with sdLDL, F&F was more efficient in reducing TG and increasing LDL radius.

Keywords atherogenic lipoprotein phenotype, cardiovascular disease, coronary artery disease, metabolic syndrome, small, dense LDL, type 2 diabetes.

Eur J Clin Invest 2009; 39 (6): 463–470

Introduction

Lipid metabolism in the metabolic syndrome (MS) and type 2 diabetes mellitus (T2DM) is characterized by increased triglycerides (TG), low high-density lipoprotein cholesterol (HDL-C), but only slightly elevated low-density lipoprotein cholesterol (LDL-C) levels [1]. Despite virtually normal LDL-C levels, the LDL-profile in MS/T2DM frequently shows significantly elevated levels of small, dense LDL (sdLDL) [1,2].

A link between sdLDL and increased risk of coronary artery disease (CAD) was first proposed by Austin and coworkers [3]. Subsequent case–control and prospective studies have shown that a preponderance of sdLDL increases the risk of CAD by up to sevenfold [4–6]. sdLDL exhibits reduced uptake by the LDL-receptor [7], and is more susceptible to oxidation. sdLDL may also cause endothelial dysfunction independent of other risk factors, such as LDL-C, TG and HDL-C [8]. Thus, LDL size has been classified as an emerging cardiovascular risk factor by the adult treatment panel (ATP) III [9]. Using only LDL-C levels, cardiovascular risk may be underestimated because normal or only moderate LDL-levels may mask a higher number of sdLDL particles. However, LDL-C remains the primary target of treatment in persons with sdLDL [9].

If sdLDL particles accompany elevated TG or low HDL-C in high-risk persons, it is suggested that the use of fibrates, a group of peroxisome proliferator activated receptor (PPAR)

alpha agonists, or nicotinic acid may be considered as components of lipid-lowering therapy [9]. However, similar to fibrates the PPAR gamma agonist pioglitazone reduced the amount of sdLDL particles in non-diabetic patients with hypertension [10] and in patients with T2DM [11] as well.

Although there are various studies describing the effects of statins, fibrates and nicotinic acid [12,13], there are only few data on the new cholesterol absorption inhibitor ezetimibe, with respect to its influence on individual LDL-subfractions.

Results from a trial investigating ezetimibe versus fenofibrate vs. the combination of both in patients with mixed hyperlipidaemia show that ezetimibe alone vs. placebo induced a slight improvement in LDL size compared with placebo. However, there was no additional effect on LDL size when ezetimibe was combined with fibrates [14]. Similarly, in patients with severe hypercholesterolaemia not dominated by sdLDL and treated by regular LDL apharesis and statins, the addition of ezetimibe reduced all LDL subtypes with no specific effect on sdLDL [15].

In general, the effect of lipid-lowering therapy on sdLDL is dependent on the LDL profile before treatment [16]. Therefore, this study will evaluate the effect of the combination of fluvastatin/fenofibrate compared with the combination of simvastatin/ezetimibe in patients with MS/T2DM that present either with or without sdLDL.

Materials and methods

Study design and participants

This phase IV study (ClinicalTrials.gov number, NCT00385658) was a multicentre, randomized, open-label, cross-over study initiated by Novartis Pharma AG, Basel, Switzerland, to assess the effect of the combination of fluvastatin/fenofibrate (80/200 mg day^{-1}) (F&F) on HDL-C as primary endpoint in comparison with the combination of simvastatin/ezetimibe (20/10 mg day^{-1}) (S&E) in patients with MS. LDL subfractions as a secondary endpoint measure was evaluated in a subgroup of patients.

Included were both genders aged between 18 and 75 years with MS according to the international diabetes federation (IDF) criteria [17]: low HDL-C (< 40 mg dL^{-1} (< 1·0 mmol L^{-1}) for men and < 50 mg dL^{-1} (< 1·25 mmol L^{-1}) for females, waist-circumference ≥ 94 cm for men and ≥ 80 cm for females plus one of the following criteria: TG ≥ 150 mg dL^{-1} (≥ 1·7 mmol L^{-1}), blood pressure (diastolic ≥ 85 mmHg and/or systolic ≥ 130 mmHg or anti-hypertensive therapy), fasting glucose ≥ 100 mg dL^{-1} (≥ 6 mmol L^{-1}) or prevalent T2DM. Seventy-five patients were randomized and 69 completed the study. Complete LDL-subfraction profiles of 56 patients from eight study centres were available for evaluation. From these, 28 were randomized to start with F&F for 6 weeks followed by 6 weeks treatment with S&E with a wash-out phase of 2 weeks in between, the other 28 patients started vice versa.

Laboratory procedures

At baseline and after 6 weeks of each therapy, fasting venous blood samples were drawn and immediately delivered for biochemical tests. Samples for the determination of LDL subfractions were stored for up to 1 week at 4 °C before lipoprotein separation. Previous experiments indicated that lipid and lipoprotein measurements were not affected by these conditions [18].

Lipoprotein separation. Lipoproteins were isolated by sequential preparative ultracentrifugation using the following densities: d < 1·006 kg L^{-1} for very low density lipoprotein (VLDL), 1·006 < d < 1·019 kg L^{-1} for intermediate dense lipoprotein (IDL), 1·019 < d < 1·063 kg L^{-1} for LDL and 1·063 < d < 1·21 kg L^{-1} for HDL. Total LDL (1·019 < d < 1·063 kg L^{-1}) were fractionated into six density classes by equilibrium density gradient centrifugation [19]. Density ranges of subfractions were as follows: LDL-1, < 1·031 kg L^{-1}; LDL-2, 1·031–1·034 kg L^{-1}; LDL-3, 1·034–1·037 kg L^{-1}; LDL-4, 1·037–1·040 kg L^{-1}; LDL-5, 1·040–1·044 kg L^{-1}; LDL-6, > 1·044 kg L^{-1}. Atherogenic LDL-5 and LDL-6 are summarized as sdLDL [16]. The inter-assay coefficient of variance (CV) of the determination of apolipoprotein (apo) B in each of the 6 LDL subfractions is 5% and below [18].

Lipoprotein chemistry. Cholesterol (C), free cholesterol (FC), TG and phospholipids (PL) were determined enzymatically with the CHOD-PAP, the COD-PAP and the GPO-PAP method, and by phospholipase D, cholineoxidase and peroxidase, respectively, with commercially available reagents (Wako Chemicals, Osaka, Japan). The concentration of esterified cholesterol (CE) was calculated from the difference of C and FC. Concentrations of apolipoproteins were determined by turbidimetry on an Olympus analyser AU 640 using polyclonal antisera (Rolf Greiner Biochemica, Flacht, Germany) specific for the respective antigens.

Mean low density lipoprotein diameter. The mean diameter of LDL was calculated using the molar concentrations of FC, CE, PL, TG and apoB-100 in the LDL fraction (1·019 < d < 1·063 kg L^{-1}) as validated by X-ray small-angle scattering [19]. The CV of the mean LDL diameter was around 5%.

Mean low density lipoprotein (LDL) density. The mean density of total LDL was calculated as the weighted (by apoB-100 content) mean of the densities of each of the LDL subfractions [11] according to the following equation: Mean LDL density = (apoB in LDL-1 × 1·025 + apoB in

LDL-2 × 1·0325 + apoB in LDL-3 × 1·0355 + apoB in LDL-4 × 1·0385 + apoB in LDL-5 × 1·042 + apoB in LDL-6 × 1·0535)/(apoB in total LDL) kg L^{-1}. The CV of the mean LDL diameter was around 5%.

Statistical analysis

Treatment effects were analysed according to predefined baseline sdLDL levels: patients were classified as having sdLDL at baseline (sum of apoB in LDL-5 plus LDL-6 > 250 mg L^{-1}) or as having no sdLDL at baseline (sum of apoB in LDL-5 plus LDL-6 ≤ 250 mg L^{-1}) [16]. Clinical and anthropometric characteristics of individuals grouped according to sdLDL at baseline are presented as percentages for categorical variables and as means ± standard deviations or medians and minimum/maximum for continuous variables, as appropriate. Continuous variables were analysed by the Mann–Whitney *U*-test, and categorical variables by the Fisher's exact test for differences between groups with or without sdLDL. Changes in lipid, lipoprotein and apolipoprotein levels between baseline values and values after treatment with either F&F or S&E were compared using the non-parametric Wilcoxon signed ranks test. Changes were considered statistically significant if *P*-value was < 0·05. All calculations were performed using SPSS (SPSS Inc., Chicago, IL, USA) for Windows (version 16·0).

Results

Patient characteristics at baseline

In this study investigating patients with MS/T2DM, 68% had notable levels of sdLDL (> 250 mg L^{-1} apoB in LDL-5 plus LDL-6) at baseline. In these patients, TG and total cholesterol were elevated compared with non-sdLDL patients. However, LDL-C, HDL-C and clinical characteristics were similar in both groups (Table 1). There was a high proportion of diagnosed hypertension (> 75%) in both groups which is in line with previous findings [20].

Table 1 Summary of patient demographic and clinical characteristics at baseline

	All patients (*n* = 56)	**No sdLDL* (*n* = 18)**	**sdLDL* (*n* = 38)**	**no sdLDL vs. sdLDL* (*P*-value)**
Age, years (mean ± SD)	55 ± 10	56 ± 9	55 ± 10	n.s.
Sex (female/male)	19/37	9/9	10/28	n.s.
Body mass index, kg m^{-2} (mean ± SD)	32 ± 5	31 ± 4	33 ± 5	n.s.
Waist circumference (±SD; cm)	110 ± 12	106 ± 11	111 ± 13	n.s.
HbA1c, % (mean ± SD)	6·1 ± 0·9	5·9 ± 0·9	6·1 ± 0·9	n.s.
Blood pressure systolic (±SD; mmHg)	137 ± 11	135 ± 12	139 ± 11	n.s.
Blood pressure diastolic (±SD; mmHg)	84 ± 8	84 ± 9	84 ± 8	n.s.
Lipoprotein phenotype				
Total cholesterol (±SD; mmol L^{-1})	5·61 ± 0·83	5·16 ± 0·78	5·83 ± 0·78	0·017
LDL cholesterol (±SD; mmol L^{-1})	2·65 ± 0·58	2·44 ± 0·76	2·75 ± 0·46	n.s.
Triglycerides (median; mmol L^{-1}) (minimum–maximum)	2·79 (0·64–6·49)	2·07 (0·64–6·49)	3·34 (1·28–6·00)	0·017
HDL cholesterol (±SD; mmol L^{-1})	0·91 ± 0·20	0·95 ± 0·27	0·89 ± 0·17	n.s.
apoB in small, dense LDL† (±SD; mg L^{-1})	317 ± 117	189 ± 264	378 ± 91	
History of:				
Type 2 diabetes, *n* (%)	15 (27)	4 (22)	11 (29)	n.s.
Hypertension, *n* (%)	44 (79)	14 (78)	30 (79)	n.s.
Coronary artery disease, *n* (%)	2 (4)	1 (6)	1 (3)	n.s.

n.s., not significant.
*No sdLDL and sdLDL: apoB in the LDL5 + LDL-6 fraction < 25 mg dL^{-1} and apoB in the LDL-5 + LDL-6 fraction > 25 mg dL^{-1} respectively [16].
†LDL-5 + LDL-6 fraction. Continuous variables were analysed by the Mann–Whitney *U*-test, and categorical variables by the Fisher's exact test for differences between groups with or without sdLDL.

Changes in lipids, lipoproteins and apolipoproteins

After 6 weeks of treatment, reduction of total cholesterol, LDL-C and apolipoprotein apoB-100 by S&E was stronger than by F&F in both groups (Tables 2 and 3). In patients without sdLDL, no difference with regard to TG reduction was observed (Table 2), whereas in the sdLDL group F&F was more efficient in reducing TG (Table 3). The increase of HDL-C and apoA-I was more pronounced with S&E in the non-sdLDL group (Table 2); however, in the group with sdLDL, there was no difference between treatments (Table 3). In patients with sdLDL, the cardioprotective apoA-II [21,22] was markedly increased by F&F, whereas S&E had no or only little effect (Table 3). Although only significant in sdLDL patients, the cardiovascular risk marker apoC-III [23] was more effectively reduced by F&F, while the reduction of the rather beneficial lipolytic cofactor ApoC-II was more pronounced by S&E in both patient groups (Tables 2 and 3).

LDL subfractions

Each VLDL, IDL and LDL particle contains one apoB molecule. The concentration of apoB in each lipoprotein fraction, therefore, represents the number of VLDL, IDL and LDL particles.

Table 2 Lipids, lipoproteins and apolipoproteins in patients with MS without small, dense LDL (18/56)

	Baseline	Fluvastatin & fenofibrate	Simvastatin & ezetimibe	*P*-value
CH (±SD; mmol L^{-1})	5·16 ± 0·78	4·29 ± 1·06	3·88 ± 0·90	0·043
TG (median; mmol L^{-1}) (minimum–maximum)	2·07 (0·64–6·49)	1·30 (0·71–4·94)	1·47 (0·77–4·19)	n.s.
LDL-C (±SD; mmol L^{-1})	2·44 ± 0·76	2·06 ± 0·64	1·68 ± 0·63	0·006
HDL-C (±SD; mmol L^{-1})	0·95 ± 0·27	1·03 ± 0·25	1·15 ± 0·33	0·020
ApoA-I (±SD; g L^{-1})	1·25 ± 0·15	1·24 ± 0·17	1·30 ± 0·20	0·015
ApoA-II (±SD; g L^{-1})	0·48 ± 0·06	0·56 ± 0·12	0·52 ± 0·08	n.s.
ApoB-100 (±SD; g L^{-1})	0·93 ± 0·16	0·75 ± 0·24	0·64 ± 0·16	0·020
ApoC-II (±SD; mg L^{-1})	52 ± 28	46 ± 23	40 ± 25	0·048
ApoC-III (±SD; mg L^{-1})	132 ± 60	110 ± 57	122 ± 52	n.s.

P-values were calculated by the non-parametric Wilcoxon signed ranks test for differences between treatment groups (changes between baseline and treatment).
CH, cholesterol; TG, triglycerides, LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; Apo, apolipoprotein; n.s., not significant.

Table 3 Lipids, lipoproteins and apolipoproteins in patients with MS with small, dense LDL (38/56)

	Baseline	Fluvastatin & fenofibrate	Simvastatin & ezetimibe	*P*-value
CH (±SD; mmol L^{-1})	5·83 ± 0·78	4·38 ± 0·80	3·74 ± 0·67	< 0·001
TG (median; mmol L^{-1}) (minimum–maximum)	3·34 (1·28–6·00)	1·56 (0·84–3·38)	2·00 (0·76–3·60)	0·029
LDL-C (±SD; mmol L^{-1})	2·75 ± 0·46	2·24 ± 0·46	1·64 ± 0·38	< 0·001
HDL-C (±SD; mmol L^{-1})	0·89 ± 0·17	0·99 ± 0·22	0·99 ± 0·18	n.s.
ApoA-I (±SD; g L^{-1})	1·18 ± 0·14	1·22 ± 0·18	1·22 ± 0·14	n.s.
ApoA-II (±SD; g L^{-1})	0·48 ± 0·07	0·59 ± 0·10	0·49 ± 0·07	< 0·001
ApoB-100 (±SD; g L^{-1})	1·14 ± 0·17	0·82 ± 0·18	0·69 ± 0·15	< 0·001
ApoC-II (±SD; mg L^{-1})	67 ± 27	49 ± 17	44 ± 17	0·012
ApoC-III (±SD; mg L^{-1})	180 ± 63	118 ± 37	131 ± 39	0·016

P-values were calculated by the non-parametric Wilcoxon signed ranks test for differences between treatment groups (changes between baseline and treatment).
CH, cholesterol; TG, triglycerides, LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; Apo, apolipoprotein; n.s., not significant.

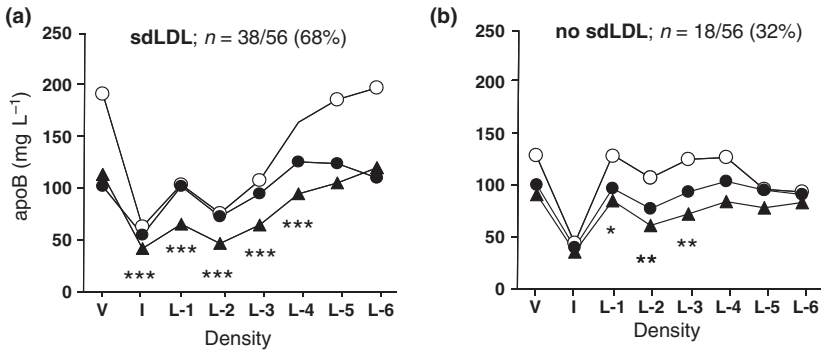

Figure 1 Mean changes in subfractions of LDL by fluvastatin/fenofibrate (80/200) (F&F) and simvastatin/ezetimibe (20/10) (S&E) in patients with the metabolic syndrome with, $n = 38$ (a); and without, $n = 18$ (b) sdLDL (apoB in LDL-5 plus LDL-6 > 250 mg L^{-1}) at baseline. White circles, baseline values; black circles, values after 6 weeks of F&F treatment; black triangles, values after 6 weeks of S&E treatment. *$P < 0{\cdot}05$; **$P < 0{\cdot}001$; ***$P < 0{\cdot}001$ for comparison between treatment changes of FF vs. SE (Wilcoxon signed ranks test).

The LDL subfraction profile of patients with sdLDL at baseline was, by definition, dominated by the densest subfractions, LDL-5 and LDL-6 (Fig. 1a). In these patients S&E lowered each of the apoB containing lipoproteins to a similar extent, whereas F&F specifically addressed sdLDL fractions LDL-5 and LDL-6, the mean percent changes from baseline of apoB were −39%, $P = 0{\cdot}001$ (VLDL); −32%, $P < 0{\cdot}001$ (IDL); −34%, $P < 0{\cdot}001$ (LDL-1); −36%, $P < 0{\cdot}001$ (LDL-2); −37%, $P < 0{\cdot}001$ (LDL-3); −40%, $P < 0{\cdot}001$ (LDL-4); −38%, $P < 0{\cdot}001$ (LDL-5) and −36%, $P < 0{\cdot}001$ (LDL-6) by S&E, and −42%, $P < 0{\cdot}001$ (VLDL); −9%, $P = 0{\cdot}026$ (IDL); ±0%, $P = 0{\cdot}712$ (LDL-1); +1%, $P = 0{\cdot}612$ (LDL-2); −6%, $P = 0{\cdot}051$ (LDL-3); −18%, $P < 0{\cdot}001$ (LDL-4); −29%, $P < 0{\cdot}001$ (LDL-5) and −41%, $P < 0{\cdot}001$ (LDL-6) by F%F respectively.

In contrast, in patients without sdLDL at baseline, the levels of the medium-dense subfractions LDL-3 and LDL-4 were higher than those of LDL-5 and LDL-6 (Fig. 1b). In these patients, both S&E and F&F decreased VLDL, IDL and LDL-1 through LDL-4 but had only marginal effect on sdLDL, if any. The mean percent changes from baseline of apoB were −23%, $P = 0{\cdot}002$ (VLDL); +2%, $P = 0{\cdot}231$ (IDL); −25%, $P = 0{\cdot}004$ (LDL-1); −33%, $P = 0{\cdot}001$ (LDL-2); −36%, $P = 0{\cdot}001$ (LDL-3); −32%, $P = 0{\cdot}001$ (LDL-4); −18%, $P = 0{\cdot}058$ (LDL-5) and −7%, $P = 0{\cdot}170$ (LDL-6) by S&E, and −15%, $P = 0{\cdot}037$ (VLDL); +8%, $P = 0{\cdot}421$ (IDL); −12%, $P = 0{\cdot}026$ (LDL-1); −15%, $P = 0{\cdot}016$ (LDL-2); −20%, $P = 0{\cdot}031$ (LDL-3); −5%, $P = 0{\cdot}074$ (LDL-4); +5%, $P = 0{\cdot}349$ (LDL-5) and +2%, $P = 0{\cdot}327$ (LDL-6) by F&F respectively.

LDL radius and density

In non-sdLDL patients, neither S&E nor F&F treatment showed any effect with regard to LDL-radius (Fig. 2) and LDL-density (Fig. 3). However, in the sdLDL group F&F effectively

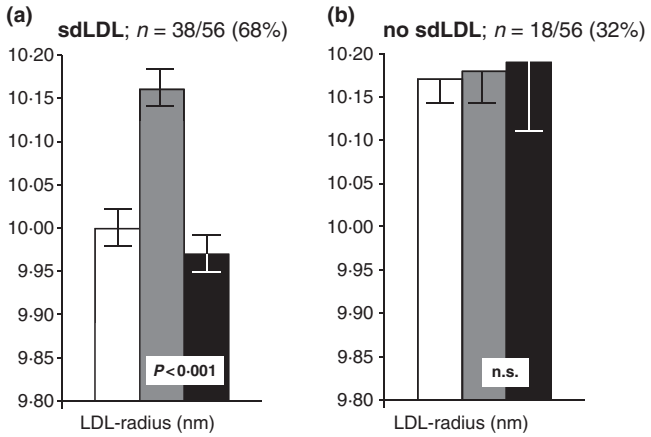

Figure 2 Mean changes in LDL radius by fluvastatin/fenofibrate (80/200) (F&F) and simvastatin/ezetimibe (20/10) (S&E) in patients with the metabolic syndrome with, $n = 38$ (a); and without, $n = 18$ (b) sdLDL (apoB in LDL-5 plus LDL-6 > 250 mg L^{-1}) at baseline. White bars, baseline values; grey bars, values after 6 weeks of F&F treatment; black bars, values after 6 weeks of S&E treatment. Comparison between treatment changes of F&F vs. S&E (Wilcoxon signed ranks test).

increased LDL-radius by 1·52%, $P < 0{\cdot}001$, and reduced LDL-density by 0·19%, $P < 0{\cdot}001$, respectively, whereas S&E had no effect at all (Fig. 3).

Safety and tolerability

None of the patients in the study experienced any serious drug-related adverse event (AE). As expected, the number of AEs was higher in the S&E group than in the F&F group. Overall, the percent of patients with AEs and myalgia was 15·1% and

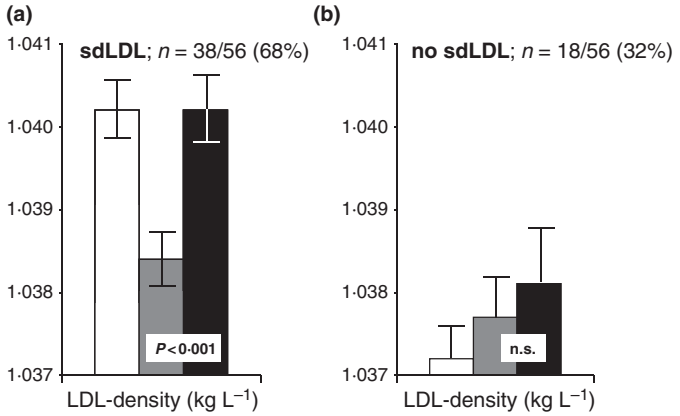

Figure 3 Mean changes in LDL density by fluvastatin/fenofibrate (80/200) (F&F) and simvastatin/ezetimibe (20/10) (S&E) in patients with the metabolic syndrome with, n = 38 (A); and without n = 18 (B) sdLDL (apoB in LDL-5 plus LDL-6 > 250 mg L^{-1}) at baseline. White bars, baseline values; grey bars, values after 6 weeks of F&F treatment; black bars, values after 6 weeks of S&E treatment. Comparison between treatment changes of F&F vs. S&E (Wilcoxon signed ranks test).

1·4% under F&F versus 22·2% and 4·2% under S&E. However, the number of patients may be too small to allow for general conclusions.

Discussion

In this study, the dosage of S&E (20/10) was not equivalent to the dosage of F&F (80/200) with respect to LDL-C lowering. Therefore, S&E was more efficient in reducing total and LDL cholesterol. This was also true for HDL-C increase in patients without sdLDL. However, in the majority of the study population presenting with sdLDL, the combination of F&F was more efficient in reducing TG and addressing LDL-quality by increasing the LDL radius – major components of the atherogenic lipoprotein phenotype (ALP). Thus, statin combination with ezetimibe shows a rather quantitative effect, whereas statin combination with fenofibrate shows a rather qualitative effect on the LDL-subfraction profile. Thus, in MS/T2DM statin combination with a fibrate appears to be more suitable to address the ALP.

sdLDLs are considered as an emerging cardiovascular risk factor [9] and are commonly encountered in subjects with the MS [1]. In this study, 68% of the patients with MS had notable levels of sdLDL. This is similar to the prevalence of 63% in non-diabetic patients with arterial hypertension [10], but less than the prevalence of 79% [16] in patients with T2DM.

In general, statins show a rather quantitative, whereas fibrates exert a rather qualitative effect on a LDL-profile dominated by sdLDL [24]. However, in contrast to the established combination of statins and fibrates, the combination of statins with the cholesterol absorption inhibitor ezetimibe is increasingly used to treat patients with MS/T2DM. The combination with statins acts synergistically in terms of LDL-C lowering: with the fixed combination of simvastatin 20 mg, up to 50% change in LDL-C may be achieved. Further, simvastatin 80 mg and simvastatin/ezetimibe 10 mg per 10 mg were equally effective in reducing fasting and post-fat load plasma lipid, and lipoprotein concentrations and lipoprotein composition in obese metabolic syndrome patients [25]. Further, combination therapy with low-dose simvastatin and ezetimibe preserved flow-mediated vasodilatation (FMD) after fat-load in contrast to high-dose simvastatin monotherapy, whereas there was no difference in FMD in the fasting state [26]. These findings are somewhat in contrast to other studies: on the basis of similar LDL-C lowering, only simvastatin improved endothelial function as measured by FMD but ezetimibe did not [27]. However, in contrast to statins and fibrates, no cardiovascular morbidity/mortality studies for ezetimibe are yet available. Using intima media thickness as surrogate parameter, the ENHANCE trial showed that there was no improvement by additional administration of ezetimibe although LDL-C, TG and sCRP were lowered more efficiently than with simvastatin treatment alone [28].

Although statins are recommended in diabetic dyslipidaemia to achieve LDL-C goals below 100 mg dL^{-1} and the combination of statin plus ezetimibe being even more efficacious in reducing LDL-C, the combination of statin plus fibrate might be better tailored to treat the specific dyslipidaemia in MS/T2DM as compared with statins plus ezetimibe. Combined treatment with simvastatin and ciprofibrate was shown to increase LDL particle size in patients with familial combined hyperlipidaemia and CAD [29]. Therefore, in NCEP ATPII, the combination of statins with fibrates is recommended in diabetic dyslipidaemia [9].

In fact, recent subgroup analysis from the FIELD trial suggests that the clinical benefit of fenofibrate seems indeed to be greater in patients with the MS. Fenofibrate significantly reduced cardiovascular disease (CVD) events in those with low-HDL-C or hypertension. However, the largest effect to reduce CVD risk was observed in subjects with marked dyslipidaemia, where a 27% relative risk reduction with a number needed to treat of 23 was observed [30].

Fluvastatin has been proven to reduce cardiovascular (CVD) risk effectively in patients with the MS as well. In fact, in a pooled analysis of more than 7000 individuals from 30 completed trials, patients with the MS had a greater reduction of TG and a greater increase of HDL-C, which resulted in lower incidences of major adverse cardiovascular events (MACEs) and an increase in the time to first MACE [31]. In line,

fluvastatin has been shown to reduce sdLDL and to increase HDL-C [16,32]. Regarding drug-safety and risk of myopathy, there is evidence that particularly the combination of fluvastatin with fenofibrate seems to have a relatively low risk [33,34]. Similarly, in this study, the combination of fluvastatin/fenofibrate appeared to be superior for the treatment of the specific dyslipidaemia encountered in the MS/T2DM as compared with simvastatin/ezetimibe, although the small number of patients may not allow for generalization. Further, the pro-atherogenic apoC-III [23] and the anti-atherogenic apoA-II [21,22] were both changed in a favourable way by F&F only possibly translating in even further clinical benefit.

Our study has certain limitations: the study design used different statins with dosages of different LDL-C lowering potential, making a direct comparison of treatment groups difficult. Further, there were only a limited number (56) of patients available. These have been even further stratified into 38 patients with sdLDL and 18 patients without sdLDL. However, the ultracentrifugation methodology used for LDL subfractionation is very robust. Thus, even on the basis of such low patient numbers per group, the study results are sound.

In conclusion, combination therapy of simvastatin plus ezetimibe was more efficient in reducing total cholesterol and LDL cholesterol. This was also true for increasing HDL cholesterol in patients without small, dense LDL particles. However, the majority of patients with the metabolic syndrome presented with small, dense LDL particles. In these patients, the combination therapy of fluvastatin plus fenofibrate was more efficient in improving components of the atherogenic lipoprotein phenotype, namely, triglycerides and LDL radius. Thus, statin combination with a fibrate appears to be better suited to address the characteristic dyslipidaemia in the metabolic syndrome than statin combination with ezetimibe.

Funding

This study was supported by Novartis Pharma, Germany.

Disclosures

None to declare.

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Received 29 October 2008; accepted 2 February 2009

References

1 Haffner SM. Management of dyslipidemia in adults with diabetes. *Diabetes Care* 1998;**21**:160–78.
2 Reaven GM, Chen Y-DI, Jeppesen J, Maheux P, Krauss RM. Insulin resistance and hyperinsulinemia in individuals with small, dense, low density lipoprotein particles. *J Clin Invest* 1993;**92**:141–6.
3 Austin MA, Breslow JL, Hennekens CH, Buring JE, Willett WC, Krauss RM. Low-density lipoprotein subclass patterns and risk of myocardial infarction. *J Am Med Assoc* 1988;**260**:1917–21.
4 Austin MA, King M-C, Vranizian KM, Krauss RM. Atherogenic lipoprotein phenotype: a proposed genetic marker for coronary heart disease risk. *Circulation* 1990;**82**:495–506.
5 Griffin BA, Freeman DJ, Tait GW, Thomson J, Caslake MJ, Packard CJ *et al.* Role of plasma triglyceride in the regulation of plasma low density lipoprotein (LDL) subfractions: relative contribution of small, dense LDL to coronary heart disease risk. *Atherosclerosis* 1994;**106**:241–53.
6 St-Pierre AC, Cantin B, Dagenais GR, Mauriege P, Bernard PM, Despres JP *et al.* Low-density lipoprotein subfractions and the long-term risk of ischemic heart disease in men: 13-year follow-up data from the Quebec Cardiovascular Study. *Arterioscler Thromb Vasc Biol* 2005;**25**:553–9.
7 Nigon F, Lesnik P, Rouis M, Chapman MJ. Discrete subspecies of human low density lipoproteins are heterogeneous in their interaction with the cellular LDL receptor. *J Lipid Res* 1991;**32**:1741–53.
8 Vakkilainen J, Makimattila S, Seppala-Lindroos A, Vehkavaara S, Lahdenpera S, Groop PH *et al.* Endothelial dysfunction in men with small LDL particles. *Circulation* 2000;**102**:716–21.
9 Third Report of the National Cholesterol Education Program (NCEP). Expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III) final report. *Circulation* 2002;**106**:3143–421.
10 Winkler K, Konrad T, Füllert S, Friedrich I, Destani R, Baumstark MW *et al.* Pioglitazone reduces atherogenic dense LDL particles in nondiabetic patients with arterial hypertension. a double-blind, placebo-controlled study. *Diabetes Care* 2003;**26**:2588–94.
11 Winkler K, Friedrich I, Baumstark MW, Wieland H, März W. Pioglitazone reduces atherogenic dense low density lipoprotein (LDL) particles in patients with type 2 diabetes mellitus. *Br J Diabetes Vasc Dis* 2002;**2**:143–8.
12 Chapman MJ, Guerin M, Bruckert E. Atherogenic, dense low-density lipoproteins. Pathophysiology and new therapeutic approaches. *Eur Heart J* 1998;**19**(Suppl. A):A24–30.
13 Berneis K, Rizzo M. LDL size: does it matter? *Swiss Med Wkly* 2004;**134**:720–4.
14 Farnier M, Freeman MW, Macdonell G, Perevozskaya I, Davies MJ, Mitchel YB *et al.* Efficacy and safety of the coadministration of ezetimibe with fenofibrate in patients with mixed hyperlipidaemia. *Eur Heart J* 2005;**26**:897–905.

15 Geiss HC, Otto C, Parhofer KG. Effect of ezetimibe on low-density lipoprotein subtype distribution: results of a placebo-controlled, double-blind trial in patients treated by regular low-density lipoprotein apheresis and statins. *Metabolism* 2006;**55**:599–604.
16 Winkler K, Abletshauser C, Hoffmann MM, Friedrich I, Baumstark MW, Wieland H *et al*. Effect of fluvastatin slow-release on low-density lipoprotein (LDL) subfractions in patients with type 2 diabetes mellitus: baseline LDL profile determines specific mode of action. *J Clin Endocrinol Metab* 2002;**87**:5485–90.
17 Alberti KG, Zimmet P, Shaw J. The metabolic syndrome–a new worldwide definition. *Lancet* 2005;**366**:1059–62.
18 Winkler K, Wetzka B, Hoffmann MM, Friedrich I, Kinner M, Baumstark MW *et al*. Low density lipoprotein (LDL) subfractions during pregnancy: accumulation of buoyant LDL with advancing gestation. *J Clin Endocrinol Metab* 2000;**85**:4543–50.
19 Baumstark MW, Kreutz W, Berg A, Frey I, Keul J. Structure of human low-density lipoprotein subfractions, determined by X-ray small-angle scattering. *Biochim Biophys Acta* 1990;**1037**:48–57.
20 Isomaa B, Almgren P, Tuomi T, Forsen B, Lahti K, Nissen M *et al*. Cardiovascular morbidity and mortality associated with the metabolic syndrome. *Diabetes Care* 2001;**24**:683–9.
21 Birjmohun RS, Dallinga-Thie GM, Kuivenhoven JA, Stroes ES, Otvos JD, Wareham NJ *et al*. Apolipoprotein A-II is inversely associated with risk of future coronary artery disease. *Circulation* 2007;**116**:2029–35.
22 Winkler K, Hoffmann MM, Seelhorst U, Wellnitz B, Boehm BO, Winkelmann BR *et al*. Apolipoprotein A-II is a negative risk indicator for cardiovascular and total mortality: findings from the Ludwigshafen Risk and Cardiovascular Health Study. *Clin Chem* 2008;**54**:1405–6.
23 Scheffer PG, Teerlink T, Dekker JM, Bos G, Nijpels G, Diamant M *et al*. Increased plasma apolipoprotein C-III concentration independently predicts cardiovascular mortality: the Hoorn Study. *Clin Chem* 2008;**54**:1325–30.
24 Winkler K, Weltzien P, Friedrich I, Schmitz H, Nickell H, Hauck P *et al*. Qualitative effect of fenofibrate and quantitative effect of atorvastatin on LDL profile in combined hyperlipidemia with dense LDL. *Exp Clin Endocrinol Diabetes* 2004;**112**:241–7.
25 Hajer GR, Dallinga-Thie GM, van Vark-van der Zee LC, Visseren FL. The effect of statin alone or in combination with ezetimibe on postprandial lipoprotein composition in obese metabolic syndrome patients. *Atherosclerosis* 2009;**202**:216–24.
26 Olijhoek JK, Hajer GR, van der Graaf Y, Dallinga-Thie GM, Visseren FL. The effects of low-dose simvastatin and ezetimibe compared to high-dose simvastatin alone on post-fat load endothelial function in patients with metabolic syndrome: a randomized double-blind crossover trial. *J Cardiovasc Pharmacol* 2008;**52**:145–50.
27 Landmesser U, Bahlmann F, Mueller M, Spiekermann S, Kirchhoff N, Schulz S *et al*. Simvastatin versus ezetimibe: pleiotropic and lipid-lowering effects on endothelial function in humans. *Circulation* 2005;**111**:2356–63.
28 Kastelein JJ, Akdim F, Stroes ES, Zwinderman AH, Bots ML, Stalenhoef AF *et al*. Simvastatin with or without ezetimibe in familial hypercholesterolemia. *N Engl J Med* 2008;**358**:1431–43.
29 Kontopoulos AG, Athyros VG, Papageorgiou AA, Hatzikonstandinou HA, Mayroudi MC, Boudoulas H. Effects of simvastatin and ciprofibrate alone and in combination on lipid profile, plasma fibrinogen and low density lipoprotein particle structure and distribution in patients with familial combined hyperlipidaemia and coronary artery disease. *Coron Artery Dis* 1996;**7**:843–50.
30 Scott R, O'Brien R, Fulcher G, Pardy C, d'Emden M, Tse D *et al*. The effects of fenofibrate treatment on cardiovascular disease risk in 9795 people with type 2 diabetes and various components of the metabolic syndrome: the FIELD study. *Diabetes Care* 2009;**32**:493–8.
31 Winkler K, Ablethauser CB, Gimpelewicz C, Bortolini M, Isaacsohn JL. Risk reduction and tolerability of fluvastatin in patients with the metabolic syndrome: a pooled analysis of thirty clinical trials. *Clin Ther* 2007;**29**:1987–2000.
32 Ballantyne CM, Herd JA, Ferlic LL, Dunn JK, Farmer JA, Jones PH *et al*. Influence of low HDL on progression of coronary artery disease and response to fluvastatin therapy. *Circulation* 1999;**99**:736–43.
33 Jones PH, Davidson MH. Reporting rate of rhabdomyolysis with fenofibrate + statin versus gemfibrozil + any statin. *Am J Cardiol* 2005;**95**:120–2.
34 Farnier M, Bortolini M, Salko T, Freudenreich MO, Isaacsohn JL, Troendle AJ *et al*. Frequency of creatine kinase elevation during treatment with fluvastatin in combination with fibrates (bezafibrate, fenofibrate, or gemfibrozil). *Am J Cardiol* 2003;**91**:238–40.

