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ORIGINAL ARTICLE

Efficacy and safety of ezetimibe/simvastatin association on non-diabetic and diabetic patients with polygenic hypercholesterolemia or combined hyperlipidemia and previously intolerant to standard statin treatment

G. Derosa* MD PhD, A. D'Angelo* BD PhD, I. G. Franzetti† MD, P. D. Ragonesi‡ MD, G. Gadaleta§ MD, F. Scalise¶ MD, L. Ciccarelli** MD, M. N. Piccinni†† MD and A. F. G. Cicero‡‡ MD

**Department of Internal Medicine and Therapeutics, University of Pavia, Pavia, Italy, †Metabolic Unit, Regional Hospital, Varese, Italy, ‡Diabetes Care Unit, S. Carlo Hospital, Milano, Italy, §Division of Medicine, Civic Hospital, Cittiglio, Varese, Italy, ¶Cardiovascular Department, Policlinico of Monza, Monza, Italy, **RSA Don Leone Porta, Milano, Italy, ††Fondazione Ospedale della Carità, Casalbuttano (CR), Italy and ‡‡''G. Descovich'' Atherosclerosis Study Center, ''D. Campanacci'' Clinical Medicine and Applied Biotechnology Department, University of Bologna, Bologna, Italy*

SUMMARY

Background and objective: **One of the problems associated with reaching the low-density lipoprotein cholesterol (LDL-C) target during statin treatment is the emergence of laboratory or clinical side effects. The aim of our study was to evaluate the prevalence of statin-associated adverse events in diabetic and non-diabetic patients affected by polygenic hypercholesterolemia or combined hyperlipidemia and the efficacy and tolerability of treatment with ezetimibe/simvastatin 10/10 mg/day on the same subjects experiencing the adverse events.**

Methods: **Consecutively enrolment of patients affected by polygenic hypercholesterolemia or combined hyperlipidemia with or without type 2 diabetes mellitus. Each Centre used any of the available statins on the basis of current clinical judgement and monitored enrolled patients for adverse events during the following 2 years. Those patients with moderate adverse events suspended the current statin therapy for 1 month (washout period), and then were shifted to treatment with ezetimibe/simvastatin 10/10 mg/day and again monitored for adverse events in the following 6 months. We assessed body mass index, glycated haemoglobin, fasting plasma glucose, total cholesterol, LDL-C, high-density lipoprotein cholesterol, triglycerides, alanine aminotransferase, aspartate aminotransferase, creatinine phosphokinase and monitored adverse events such as asthenia and myalgia.**

Results and discussion: **All 1170 Caucasian patients affected by polygenic hypercholesterolemia obtained a significant reduction in LDL-C during the observation period ($P < 0{\cdot}05$), while those with combined hyperlipidemia also showed a reduction in TG plasma level ($P < 0{\cdot}05$) and a significant increase in HDL-C ($P < 0{\cdot}05$). Patients affected by polygenic hypercholesterolemia experiencing adverse event under statin treatment obtained a significantly lower reduction than those tolerating the treatment ($P < 0{\cdot}001$). The prevalence of adverse events under statin treatment was 4·9% in non-diabetic patients with polygenic hypercholesterolemia, 8·6% in those with combined hyperlipidemia, 7·1% in diabetic patients with polygenic hypercholesterolemia and 7·6% in those with combined hyperlipidemia. Six months after the shift to treatment with ezetimibe/simvastatin 10/10 mg, all patients experienced a significant improvement in LDL-C, TG and HDL-C plasma level. No**

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Correspondence: Giuseppe Derosa, MD, PhD, Department of Internal Medicine and Therapeutics, University of Pavia, P.le C. Golgi, 2-27100 Pavia, Italy. Tel.: +39 0382 526217; fax: +39 0382 526259; e-mail: giuseppe.derosa@unipv.it

adverse event was registered during the ezetimibe/simvastatin 10/10 mg treatment period. It seems that previous side effects observed with statins did not re-appear with the administration of ezetimibe/simvastatin 10/10 mg/day.
Conclusions: **The efficacy and adverse effect profile of the ezetimibe and simvastatin combination appear to be good for both diabetic and non-diabetic patients, and in both conditions.**

Keywords: **combined hyperlipidemia, ezetimibe, poligenic hypercholesterolemia, simvastatin, type 2 diabetes mellitus**

INTRODUCTION

Lowering of low-density lipoprotein cholesterol (LDL-C) with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) is clearly efficacious in the primary and secondary prevention of coronary artery disease and cerebrovascular disease (1, 2).

However, despite increasing use of statins, a significant number of coronary events still occur and many of such events take place in patients presenting with type 2 diabetes and metabolic syndrome, typically characterized by an atherogenic dyslipidemia (3).

Thus, guidelines from the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) focus on the need for intensive effort to lower LDL-C in those patients at the greatest risk of a major clinical coronary event. The guidelines suggest aiming for the ambitious target of <100 mg/dL (or even in special cases <70 mg/dL) in high-risk patients. This objective is really hard to achieve with statins alone (4). Moreover, the NCEP ATP III suggests that patients with high cardiovascular risk have to reach optimal plasma levels of triglycerides (TG) (<150 mg/dL) and high-density lipoprotein cholesterol (HDL-C, >50 mg/dL) as well (5). High risk patients are generally significantly undertreated for hypercholesterolemia both in Europe and in the US (6, 7).

One of the problems in reaching LDL-C target is the emergence of laboratory or clinical side effects during statin treatment. The prevalence of the side effects is related to the statin dosage, and to some characteristics of the patient (age, renal and liver functionality, number of concomitant drugs consumed, glucose tolerance, etc) (8).

The recently introduced ezetimibe, a highly selective and generally well-tolerated inhibitor of dietary and biliary cholesterol absorption, appears to be an interesting add-on therapy to low-dose statins to obtain significant improvement in different lipid parameters without increasing the dose and hence the dose-related statin side effects (9).

The aim of our study was to evaluate the prevalence of statin-associated adverse events in a large sample of diabetic and non-diabetic patients affected by polygenic hypercholesterolemia or combined hyperlipidemia and the efficacy and tolerability of a treatment with ezetimibe/simvastatin 10/10 mg/day on the same subjects experiencing the adverse events.

PATIENTS AND METHODS

Study design

This multi-centre, open, sequential controlled trial was conducted in eight Italian Lipid and Diabetes Centres. The study protocol was approved at each site by institutional review boards and was conducted in accordance with the Declaration of Helsinki and its amendments. All patients provided written informed consent.

Patients

We consecutively enrolled 1170 Caucasian patients aged ≥18 of either sex affected by polygenic hypercholesterolemia (PH, no.: 592) or combined hyperlipidemia (CH, no.: 578), (defined by ILIB, International Lipid Information Bureau) (10) with or without type 2 diabetes mellitus. The main characteristics of the studied population are reported in Table 1.

Each centre used all the available statins on the basis of the current clinical judgement (Table 2) and monitored them for adverse events during the following 2 years. Then, those patients with moderate adverse events stopped their current statin therapy for 1 month (washout period), before being shifted to treatment with ezetimibe/simvastatin 10/10 mg/day. They were again monitored for eventual adverse events in the following 6 months. Concomitant therapies had to be stabilized for at

Table 1. Baseline characteristics of the screened population

	Diabetic group	Non-diabetic group
	Baseline	Baseline
n	597	573
Sex (M/F)	293/304	280/293
Age (years)	53 ± 5	51 ± 4
Diabetes duration (years)	5 ± 3	–
BMI (kg/m^2)	28·3 ± 1·1	27·6 ± 0·8*
HbA_{1c} (%)	7·3 ± 0·6	5·0 ± 0·6***
FPG (mg/dL)	139 ± 12	88 ± 7*
SBP (mmHg)	132 ± 6	128 ± 5*
DBP (mmHg)	88 ± 4	83 ± 3*
Concomitant disease (*n*) (M/F) (%)		
Poligenic hypercholesterolemia	252 (133/119) (42·2)	340 (174/166) (59·3)*
Combined hyperlipidemia	345 (171/174) (57·8)	233 (113/120) (40·7)*
Hypertension	546 (287/259) (91·5)	186 (97/89) (32·5)***
CHD	91 (41/50) (15·2)	26 (16/10) (4·5)***

HbA_{1c}, glycated haemoglobin; FPG, fasting plasma glucose; SBP, systolic blood pressure; DBP, diastolic blood pressure; CHD, coronary heart disease.
*$P < 0·05$ vs. diabetic group; **$P < 0·01$ vs. diabetic group; ***$P < 0·001$ vs. diabetic group.

Table 2. Statins and dosages assumed by diabetic and non-diabetic patients at the baseline

		Diabetic patients				Non-diabetic patients			
Statins (type)	Dose (mg)	Patients by statin (*n*)	Patients by dosage (*n*)	PH patients (*n*)	CH patients (*n*)	Patients by statin (*n*)	Patients by dosage (*n*)	PH patients (*n*)	CH patients (*n*)
Lovastatin	20	15	6	3	3	13	5	2	3
	40		9	4	5		8	3	5
Pravastatin	20	35	12	8	4	38	16	9	7
	40		23	10	13		18	10	8
Simvastatin	20	168	66	29	37	186	79	48	31
	40		102	48	54		107	60	47
Fluvastatin	40	86	19	12	7	81	11	7	4
	80		67	45	22		70	41	29
Atorvastatin	10	134	54	20	34	155	69	39	30
	20		64	28	36		56	20	36
	40		16	6	10		30	13	17
Rosuvastatin	5	97	16	6	10	100	24	10	14
	10		66	25	41		57	20	37
	20		8	2	6		10	2	8
	40		7	2	5		9	3	6

PH, polygenic hypercholesterolemia; CH, combined hyperlipidemia.

least 3 months prior to enrolment and were resumed as shown in Table 3.

Assessments

Data collected from each patients were: Glycated haemoglobin (HbA_{1c}), fasting plasma glucose, total cholesterol (TC), LDL-C, HDL-C, TG, alanine aminotransferase, aspartate aminotransferase, creatinine phosphokinase and trained medical personnel asked patients about subjective adverse events such as aesthenia and myalgia. We also recorded body mass index, systolic blood pressure, and diastolic blood pressure.

All plasmatic variables were determined after a 12-h overnight fast. Venous blood samples were drawn from all patients between 8·00 and 9·00 hours. We used plasma obtained by addition of Na_2–EDTA, 1 mg/mL, and centrifuged at 3000 *g* for 15 min at 4 °C. Immediately after centrifugation, the plasma samples were frozen and stored at −80 °C for ≤3 months. All measurements were performed in a central laboratory.

Laboratory technicians drew blood samples and the biologist responsible for the laboratory performed the assays. HbA_{1c} level was measured using high-performance liquid chromatography (DIAMAT; Bio-Rad Laboratories, Inc., Hercules, CA, USA; normal value, 4·2–6·2%), with intra- and interassay coefficients of variation (CsV) of <2% (11). Plasma glucose was assayed using a glucose-oxidase method (GOD/PAP; Roche Diagnostics, Mannheim, Germany) with intra- and interassay CsV <2% (12). TC and TG levels were determined using fully enzymatic techniques (13, 14) on a clinical chemistry analyzer (Hitachi 737; Hitachi, Tokyo, Japan); intra- and interassay CsV were 1·0 %and 2·1% for TC measurement, and 0·9% and 2·4% for TG measurement, respectively. HDL-C level was measured after precipitation of plasma apo B-containing lipoproteins with phosphotungstic acid (15); intra- and interassay CsV were 1·0%

Table 3. Concomitant therapy at baseline by diabetic and non-diabetic patients (in brackets is reported the M:F ratio)

	Diabetic patients		Non-diabetic patients	
Therapy (M/F)	PH (252)	CH (345)	PH (340)	CH (233)
OHA	**469 (239/230)**	**559 (285/274)**	**–**	**–**
Sulphonylureas	126 (61/65)	138 (72/66)	–	–
Biguanides	146 (75/71)	179 (86/93)	–	–
Glinides	58 (30/28)	75 (41/34)	**–**	**–**
α-glucosidase-inhibitors	46 (24/22)	52 (28/24)	–	–
Thiazolidinediones	93 (49/44)	115 (58/57)	–	–
Insulin	**21 (11/10)**	**33 (15/18)**	–	–
Anti-aggregants	**230 (116/114)**	**309 (150/159)**	**228 (117/111)**	**202 (91/111)**
ASA	192 (98/94)	264 (130/134)	207 (109/98)	189 (98/91)
Ticlopidine	38 (18/20)	45 (20/25)	21 (8/13)	13 (6/7)
Anti-hypertensives	**471 (240/231)**	**577 (285/292)**	**146 (75/71)**	**121 (60/61)**
Sartans	63 (31/32)	84 (40/44)	26 (12/14)	23 (11/12)
ACE-I	131 (66/65)	156 (76/80)	47 (26/21)	36 (20/16)
Ca-antagonists	74 (39/35)	92 (47/45)	18 (9/9)	20 (9/11)
β-blockers	120 (64/56)	148 (75/73)	21 (10/11)	18 (10/8)
Diuretics	83 (40/43)	97 (47/50)	34 (18/16)	24 (10/14)
Anti-arrhythmics[a]	**21 (12/9)**	**34 (18/16)**	**4 (3/1)**	**5 (2/3)**
Nitrates	**19 (9/10)**	**12 (7/5)**	**6 (2/4)**	**4 (3/1)**
Anti-coagulants	**10 (4/6)**	**14 (7/7)**	**4 (2/2)**	**3 (1/2)**
Omega-3[b]	**43 (22/21)**	**48 (23/25)**	**14 (6/8)**	**12 (7/5)**

PH, polygenic hypercholesterolemia; CH, combined hyperlipidemia; OHA, oral hypoglycemic agents.
[a]Excluded β-blockers and Ca-antagonists; [b]Anti-arrhythmic dose (1 g/day).
Bold values indicates total number of patients in each therapy group.

Table 4. Plasma lipid levels before wash-out in patients not experiencing and experiencing adverse events during statin treatment

Patients not experiencing adverse events	Diabetic patients						Non-diabetic patients					
	Polygenic hypercholesterolemia (no. 234)			Combined hyperlipidemia (no. 319)			Polygenic hypercholesterolemia (no. 323)			Combined hyperlipidemia (no. 213)		
	Baseline	1 year	2 years	baseline	1 year	2 years	Baseline	1 year	2 years	Baseline	1 year	2 years
TC (mg/dL)	217 ± 18	176 ± 12*	167 ± 11**	225 ± 23	196 ± 16	182 ± 14*	244 ± 28	213 ± 16*	191 ± 14**	239 ± 30	202 ± 15*	192 ± 14**
LDL-C (mg/dL)	160 ± 11	121 ± 7*	110 ± 6**	139 ± 9	119 ± 6	107 ± 5*	181 ± 14	152 ± 9*	130 ± 8**	154 ± 9	125 ± 7*	115 ± 5**
HDL-C (mg/dL)	35 ± 4	39 ± 7	40 ± 8*	34 ± 5	37 ± 6	38 ± 7*	39 ± 7	40 ± 8	42 ± 9	33 ± 4	35 ± 5	38 ± 6*
Tg (mg/dL)	112 ± 31	92 ± 25	87 ± 20	258 ± 49^	202 ± 38*°	187 ± 35**£	121 ± 33	106 ± 28	94 ± 26	261 ± 51^	210 ± 40*°	193 ± 37**£
Patients experiencing adverse events	Diabetic patients						Non-diabetic patients					
	Polygenic hypercholesterolemia (no. 18)			Combined hyperlipidemia (no. 26)			Polygenic hypercholesterolemia (no. 17)			Combined hyperlipidemia (no. 20)		
	Baseline	1 year	2 years	Baseline	1 year	2 years	Baseline	1 year	2 years	Baseline	1 year	2 years
TC (mg/dL)	223 ± 25	203 ± 15	192 ± 13*	240 ± 30	218 ± 23*	196 ± 14**	238 ± 29	209 ± 18*	187 ± 12**	251 ± 38	221 ± 26*	202 ± 18**
LDL-C (mg/dL)	164 ± 11	145 ± 9*	134 ± 8**	159 ± 10	142 ± 9	123 ± 7*	180 ± 14	143 ± 9*	133 ± 8**	169 ± 11	142 ± 9	125 ± 7*
HDL-C (mg/dL)	33 ± 5	34 ± 6	35 ± 7	35 ± 6	37 ± 7	39 ± 8*	35 ± 7	37 ± 8	38 ± 9	34 ± 5	36 ± 7	38 ± 9*
Tg (mg/dL)	131 ± 37	122 ± 34	113 ± 30	228 ± 42[a]	194 ± 35[b]	168 ± 28*[c]	114 ± 32	93 ± 26	81 ± 20	241 ± 46[a]	217 ± 33[b]	195 ± 31*[c]

TC, total cholesterol; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; TG: triglycerides.

[a]$P < 0{\cdot}05$ vs. baseline poligenic hypercholesterolemia group; [b]$P < 0{\cdot}05$ vs. 1 year poligenic hypercholesterolemia; [c]$P < 0{\cdot}05$ vs. 2 years poligenic.

*$P < 0{\cdot}05$ vs. baseline; **$P < 0{\cdot}01$ vs. baseline.

and 1·9%, respectively. LDL-C level was calculated using the Friedewald formula (16). Body mass index was calculated by the investigators as weight in kilograms divided by the square of height in metres.

Blood pressure (BP) measurements were obtained for each patient (using the right arm) in the seated position, using a standard mercury sphygmomanometer (Erkameter 3000; ERKA, Bad Tolz, Germany) (Korotkoff I and V) with a cuff of appropriate size. BP was measured by the same investigator at each visit, in the morning before daily drug intake and after the patient had rested for ≥10 min in a quiet room. Three successive BP readings were obtained at 1-min intervals, and the mean of the three readings was calculated.

Statistical analysis

Patients data were sampled and encoded in a database and statistically analysed using the Statistical Package for Social Sciences software version 11.0 (SPSS Inc., Chicago, IL, USA). A complete descriptive analysis of all available parameters was carried out (17). Then, continuous and normally distributed parameters for the two groups (diabetics vs. non-diabetics; PH vs. CH) were compared by ANOVA followed by *t*-test for unpaired and paired samples, respectively. Categorical data for non-continuous parameters were compared with chi-square test followed by Fischer exact test. A *P*-level of <0·05 was considered significant for all test. Data are presented as mean (SD).

RESULTS

Table 4 summarizes the lipid values of the patients not experiencing and experiencing adverse event during statin treatment. All patients affected by PH obtained a significant reduction of LDL-C during the observation period ($P < 0{\cdot}05$), while those with CH also obtained a reduction in TG plasma level ($P < 0{\cdot}05$) and a significant increase in HDL-C ($P < 0{\cdot}05$). Patients affected by PH experiencing adverse event under statin treatment obtained a significantly lower reduction than those tolerating the treatment (50 ± 8 mg/dL vs. 30 ± 9 mg/dL, $P < 0{\cdot}001$).

The distribution of adverse events in the studied population sample is summarized in Table 5. Only lovastatin was associated with a higher prevalence of adverse events than other statins ($P < 0{\cdot}05$) (Fig. 1). No other significant difference was observed between subgroups. The prevalence of adverse events with statin treatment was 4·9% in non-diabetic patients with PH, 8·6% in those with CH, 7·1% in diabetic patients with PH, and 7·6% in those with CH. No statistically significant difference was observed in rates of adverse events in the considered subgroups (*P* always >0·05).

Six months after the shift to treatment with ezetimibe/simvastatin 10/10 mg, all the patients experienced a significant improvement in LDL-C, TG and HDL-C plasma level, without any significant difference between subgroups (*P* always >0·05) (Table 6). No adverse event was registered during the ezetimibe/simvastatin 10/10 mg treatment period. No significant differences were observed when statistical analyses were repeated with stratification by sex.

DISCUSSION

Statins adherence to treatment decreases to one-third, 3 years after initiation and this is the worst among cardiovascular preventive drugs (18). This is often due to underevaluated statin related side effects, often judged to be not clinically-relevant. In fact, although generally low, the prevalence of statin-related side effects reported in clinical trials is usually significantly lower to that reported in administrative databases (8) and by pharmacovigilance services (19). This is mainly due to the strict selection criteria used and the intensive follow-up of the patients in clinical trials. Moreover, both general physicians and patients may assign higher significance to mild-to-moderate increases in laboratory parameters than specialists do. They are also influenced by sources of information other than drug data-sheets, and stop therapy earlier than desirable. Therefore, for a number of patients, it is difficult to discriminate between an adverse event caused by statin treatment and one arising from unmasking of a pre-existing condition, such as hepatopathy or myopathy (20, 21).

In our study, carried out in every day clinical practice, we observed that during a period of 2 years, about 7% of subjects experienced a laboratory or clinical adverse event related to the statins (8, 19), sufficient to induce the clinician or the

Table 5. Type of adverse events recorded for enrolled patients by subgroup

	Diabetic group		Non-diabetic group	
Type of dyslipidemia	PH	CD	PH	CD
n	18	26	17	20
ALT increase (%)	50·0	37·5	35·3	55·0
≥3 × ULN [m ± SD(U/L)]	6 (153 ± 15)	6 (157 ± 16)	3 (150 ± 14)	5 (146 ± 13)
≥5 × ULN [m ± SD(U/L)]	3 (236 ± 22)	5 (219 ± 18)	3 (224 ± 19)	6 (232 ± 20)
AST increase (%)	33·3	37·5	47·1	25·0
≥3 × ULN [m ± SD(U/L)]	4 (138 ± 13)	6 (126 ± 11)	5 (132 ± 12)	3 (136 ± 12)
≥5 × ULN [m ± SD(U/L)]	2 (226 ± 19)	2 (228 ± 20)	3 (222 ± 18)	2 (220 ± 18)
ALT and AST increase (%)	38·8	31·3	29·4	35·0
≥3 × ULN [m ± SD(U/L)]	4 (148 ± 14 and 135 ± 13)	3 (167 ± 19 and 128 ± 12)	4 (151 ± 15 and 136 ± 13)	5 (160 ± 16 and 138 ± 13)
≥5 × ULN [m ± SD(U/L)]	3 (232 ± 20 and 220 ± 18)	2 (243 ± 25 and 236 ± 23)	1 (239 ± 23 and 244 ± 25)	2 (240 ± 24 and 238 ± 23)
CPK increase (%)	44·4	31·3	17·6	20·0
≥5 × ULN [m ± SD(U/L)]	8 (993 ± 37)	5 (984 ± 30)	3 (997 ± 38)	4 (989 ± 36)
≥10 × ULN [m ± SD(U/L)]	–	–	–	–
Astenia (%)	14 (77·7)	7 (43·8)	10 (58·8)	13 (65·0)
Mialgia (%)	7 (38·8)	6 (37·5)	6 (35·3)	8 (40·0)
Rhabdomyolysis (%)	–	–	–	–

PH, polygenic hypercholesterolemia; CH, combined hyperlipidemia; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatinine phosphokinase.

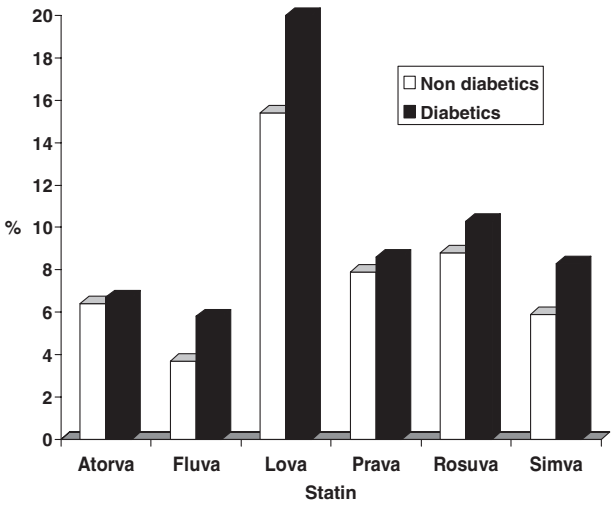

Fig. 1. Distribution of adverse events by statins treatment in non-diabetic and diabetic dyslipidemic patients.

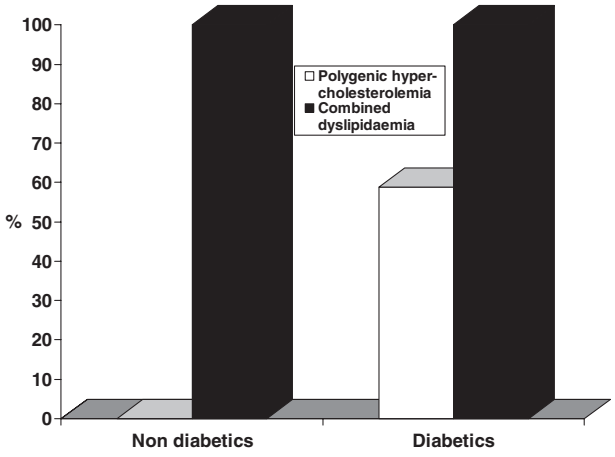

Fig. 2. Percentage of patients achieving the low-density lipoprotein cholesterol goal <100 mg/dL among those shifted to treatment with ezetimibe/simvastatin 10/10 mg 1 cp/day.

Table 6. Lipid profile at baseline, after washout (wo), and during simvastatin/ezetimibe 10/10 mg therapy in patients previously experiencing an adverse event during statin treatment

	Poligenic hypercholesterolemia				Combined hyperlipidemia			
	Baseline	After wo	3 months	6 months	Baseline	After wo	3 months	6 months
Diabetic patients								
TC (mg/dL)	192 ± 13	234 ± 29*	189 ± 12†	162 ± 10††	196 ± 14	259 ± 43*	197 ± 14†	170 ± 11††
LDL-C (mg/dL)	134 ± 8	173 ± 12*	129 ± 7†	103 ± 5††	123 ± 7	176 ± 12*	121 ± 7†	94 ± 4††
HDL-C (mg/dL)	35 ± 7	33 ± 4	36 ± 5	38 ± 8†	39 ± 8	35 ± 5	37 ± 6	40 ± 8†
Tg (mg/dL)	113 ± 30	141 ± 36	120 ± 31	103 ± 29†	168 ± 28	240 ± 43	196 ± 33†	178 ± 29††
Non-diabetic patients								
TC (mg/dL)	187 ± 12	251 ± 40*	199 ± 14†	174 ± 11††	202 ± 18	247 ± 36*	205 ± 18†	168 ± 11††
LDL-C (mg/dL)	133 ± 8	192 ± 13**	143 ± 9†	114 ± 6††	125 ± 7	163 ± 10*	129 ± 8†	90 ± 4††
HDL-C (mg/dL)	38 ± 9	34 ± 5	36 ± 5	42 ± 9††	38 ± 9	36 ± 7	38 ± 8	41 ± 9†
Tg (mg/dL)	81 ± 20	123 ± 34	102 ± 28	88 ± 22†	195 ± 31	238 ± 36	191 ± 31†	184 ± 30††

TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides.
*$P < 0{\cdot}05$ vs. baseline; **$P < 0{\cdot}01$ vs. baseline; $^{\dagger}P < 0{\cdot}05$ vs. after wo period; $^{\dagger\dagger}P < 0{\cdot}01$ vs. after wo period.

patient to change antihyperlipidemic therapy. Contrarily to reports by other authors, in our patient sample, diabetes did not appear to be associated to a higher prevalence of statin-related side effects.

The substitution of statin with ezetimibe/simvastatin 10/10 mg/day was not associated with any relevant adverse event during the 6 months of observation. Patients experienced a mean LDL-C decrease of 43%, a mean HDL-C increase of 17% and a mean TG decrease of 27·7%. These data are in agreement with that reported in a recent meta-analysis of available data (22), except for the HDL-C increase that was significantly higher in our patients. Considering the sub-classes of patients included in our study, the maximal LDL-C reduction was observed in diabetics with CH (−46.6%, the highest TG reduction and HDL-C increase in the non-diabetics with PH (−36·6% and +23.5%, respectively).

In clinical trials, the efficacy of ezetimibe in achieving the LDL-C target appears to be more relevant in diabetic patients than in non-diabetic ones (83·6% vs. 67·2%) (23). This data was confirmed by the recent VYTAL study showing that ezetimibe/simvastatin 10/20 mg reduces LDL-C [−53·6%; 95% confidence interval (CI), −55·4% to −51·8%] significantly more than atorvastatin, 10 mg/day (−38·3%; 95% CI, −40·1% to −36·5%; $P < 0{\cdot}001$) or 20 mg/day (−44·6%; 95% CI, −46·4% to −42·8%; $P < 0{\cdot}001$), and ezetimibe/simvastatin 10/40 mg (−57·6%; 95% CI, −59·4% to −55·8%) more than atorvastatin 40 (−50·9%; 95% CI, −52·7% to −49·1%; $P < 0{\cdot}001$) in hypercholesterolemic subjects affected by type 2 diabetes mellitus (24).

In our study, with the lower available dosage of the ezetimibe/simvastatin combination the LDL-C target of <100 mg/dL was achieved by 58·9% of patients. The result is good because the studied patients were all previously statin-intolerant at the doses used and their baseline LDL-C value was markedly far from the desired goal (Fig. 2).

We did not observe any adverse event related to ezetimibe/simvastatin 10/10 mg/day consumption; however, because statin side effects are not always dose-related, it is possible that if a larger cohort is studied cases of myotoxicity may appear (25).

Of course our study has limitations, such as the heterogeneity of the population sample selected with respect to hyperlipidemia and cardiovascular disease-risk level. However this is typical of studies aimed at representing the clinical practice situation. We selected a specific class of patients, previously intolerant to standard statin therapy, making it different to previous larger studies carried out in clinical practice (26). Our study does not consider possible rare adverse events such as cancer (27) for which our sample size is clearly not powered to assess.

In conclusion, on the basis of our data sampled from routine clinical practice, it seems that previously observed side effects of standard statins do not re-appear over a period of 6 months when ezetimibe/simvastatin 10/10 mg/day is introduced. The efficacy of the treatment appears to be good in both diabetic and non-diabetic patients, and in both polygenic hypercholesterolemia and combined hyperlipidemia.

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