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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

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Abstract

Ezetimibe, a cholesterol absorption inhibitor, can be combined with statins to lower low-density lipoprotein (LDL) cholesterol. We have previously shown that ezetimibe can decrease LDL cholesterol by 16% even in patients treated by regular LDL apheresis and statins (*Atherosclerosis*. 2005;180:107-112). However, it is unclear whether ezetimibe decreases all LDL subfractions equally in patients with hypercholesterolemia. We therefore evaluated the effect of ezetimibe (5 weeks, 10 mg/d) on LDL subtype distribution in a placebo-controlled, double-blind randomized crossover study in 20 patients (age, 56 ± 9 years; body mass index, 27.5 ± 4 kg/m^2) with severe hyperlipoproteinemia and coronary heart disease who are treated by statins and regular LDL apheresis. Both treatment periods (placebo and ezetimibe) were separated by a 5-week washout period. Low-density lipoprotein subtype distribution was determined at the end of each treatment period before apheresis by density gradient ultracentrifugation (LDL1, 1.020-1.024; LDL2, 1.025-1.029; LDL3, 1.030-1.034; LDL4, 1.035-1.040; LDL5, 1.041-1.047; LDL6, 1.048-1.057; LDL7, 1.058-1.066 g/mL). Overall, the LDL subtype distribution did not change significantly (large-buoyant LDL [LDL1 + LDL2], 17.2% ± 6.4% vs 16.3% ± 7.1%; intermediate LDL [LDL3 + LDL4], 49.3% ± 4.5% vs 48.2% ± 5.2%; small-dense LDL [LDL5 + LDL6 + LDL7], 33.5% ± 8.0% vs 35.5% ± 10% during placebo and ezetimibe treatments, respectively). With respect to the individual LDL subfractions, cholesterol was significantly ($P < .05$, Wilcoxon test) reduced by ezetimibe in LDL1 to LDL5 with a somewhat more pronounced reduction in larger LDL (mean ± SD, −20% ± 28%, −17% ± 32%, −14% ± 25%, −13% ± 27%, −11% ± 21%, −7% ± 21%, −4% ± 19%; median, −28%, −12%, −18%, −16%, −4%, −4%, −2% for LDL subfractions 1-7, respectively). We therefore conclude that ezetimibe decreases cholesterol in nearly all LDL subfractions. Although this was established in patients concomitantly treated with statins and apheresis, this may also hold true in other clinically relevant situations.

1. Introduction

Low-density lipoproteins (LDLs) are a heterogeneous group of particles that can be separated into several subfractions by density gradient ultracentrifugation [1] or gradient gel electrophoresis [2]. In general, small-dense LDL can be separated from intermediate and large-buoyant LDL. In vitro experiments [3-5] and epidemiologic studies [6-13] have shown that large-buoyant LDL [13,14] and particularly small-dense LDL [6-12] are more atherogenic than intermediate LDL. Such findings may be partly explained by the association of dense LDL with elevated levels of plasma triglycerides and decreased levels of high-density lipoprotein cholesterol (HDL-C) [6,15,16], Thus, small-dense LDL may reflect an abnormal metabolism of triglyceride-rich lipoproteins [15,16]. There is also evidence that additional mechanisms (eg, higher susceptibility to oxidation [3] and higher capacity to bind to intimal proteoglycans [4]) contribute to the atherogenicity of dense LDL.

The increased atherogenicity of large-buoyant LDL is less clear-cut and more difficult to explain. This association was observed in preselected patient groups [16] such as survivors from myocardial infarction with only moderate LDL hypercholesterolemia [13], whereas in a recent primary prevention study [12] it was shown that only the cholesterol content in dense LDL and not in large-buoyant LDL subfractions was associated with increased risk of CHD.

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However, independent of this ongoing dispute and of the known association of individual LDL subfractions with other lipid abnormalities, it seems that intermediate LDLs are less atherogenic than other LDL subfractions, and this may be explained by the fact that they are the optimal substrate for LDL receptors [6] and are thus more efficiently internalized than larger or more dense LDL.

As the development and progression of atherosclerosis are thus influenced by the LDL subfraction profile [6-13,15,16], it is of interest to evaluate the effect of different lipid-lowering drugs on the LDL subtype distribution. There is a number of publications describing the effects of statins, fibrates, and nicotinic acid [15,16]; however, up to now, there is only very limited data on the new cholesterol absorption inhibitor ezetimibe with respect to its influence on individual LDL subfractions. Results from one recently published study comparing ezetimibe vs fenofibrate vs ezetimibe combined with fenofibrate in patients with mixed hyperlipidemia show that ezetimibe alone vs placebo induced a slight improvement in the LDL size compared with placebo. However, there was no additional effect on LDL size when ezetimibe was combined with fibrates [17].

However, for patients with hypercholesterolemia who are good primary candidates for a combination therapy of statins with ezetimibe [18-26], there are no data on LDL subtype distribution available despite the fact that this combination is increasingly used.

We have previously shown in a placebo-controlled, double-blind, randomized crossover study that ezetimibe can decrease LDL cholesterol (LDL-C) even in patients with severe LDL hypercholesterolemia treated by regular LDL apheresis and statins [27]. In these patients, we observed an additional 16% reduction of pre- and postapheresis LDL-C. We now report the effect of ezetimibe on LDL subtype distribution in the same cohort.

2. Patients and methods

The study design is described in detail elsewhere [27]. Briefly, all patients (n = 20; age, 56 ± 9 years; M/F, 10:10; body mass index, 27.5 ± 4.0 kg/m^2) were regularly treated by LDL apheresis for at least 2 years as they failed to reach the NCEP treatment goal (<100 mg/dL/<2.6 mmol/L) during maximal dietary and drug therapy because of severe hypercholesterolemia (n = 18) or severe combined hyperlipoproteinemia (n = 2) and documented CHD. Low-density lipoprotein apheresis was done at weekly intervals in 18 patients and at biweekly intervals in 2 patients to meet this goal. Homozygous familial hypercholesterolemia was excluded on a clinical basis [27]. All patients adhered to a cholesterol-lowering diet (National Cholesterol Education Program [NCEP] Step I diet), and 19 patients were treated by statins at the maximal tolerable dose (atorvastatin, 5-80 mg/d, n = 17; simvastatin, 30-80 mg/d, n = 2). Dietary behavior, statin dose, and the apheresis technique were not changed during the study period.

The patients were randomized to receive first ezetimibe (10 mg/d) or placebo for 5 weeks in a double-blind design. After a washout period of 5 weeks, the patients were then switched to the other medication (placebo or ezetimibe) for another 5 weeks. Pre- and postapheresis cholesterol, triglycerides, very low-density lipoprotein cholesterol (VLDL-C), VLDL triglycerides, LDL-C, and HDL-C were determined at the beginning and at the end of each treatment period.

The LDL subfraction distribution was determined before apheresis during 5 weeks of placebo and during 5 weeks of ezetimibe therapy. Preapheresis LDL concentrations were used for comparison as they reflect the maximum LDL-C concentrations and thus the treatment goal. Similarly, all LDL subfractions increase to the maximum concentration before the next LDL apheresis [28]. The LDL subfractions were determined from frozen aliquots (−70°C frozen for 9 months) using density gradient ultracentrifugation, as described elsewhere [1,29]. Briefly, dry solid KBr was added to the plasma to increase its density to 1.21 g/mL. A discontinuous density gradient was constructed by 2 mL of a NaCl/KBr solution (d = 1.26 g/mL), 3 mL plasma (d = 1.21 g/mL), 2 mL of a NaCl/KBr solution (d = 1.063 g/mL), 2.5 mL of another NaCl/KBr solution (d = 1.019 g/mL), and 2 mL of a NaCl solution (d = 1.006 g/mL). All solutions contained NaN_3 (0.1%) and EDTA (0.04%). Densities were measured by a precision density meter (Anton Paar DMA 38, Graz, Austria). Ultracentrifugation was performed in a Beckmann SW 40 Ti rotor (Palo Alto, CA) at 40 000 rpm for 48 hours at 15°C. After centrifugation, total LDL was subfractionated in 7 LDL subfractions (LDL1, 1.020-1.024; LDL2, 1.025-1.029; LDL3, 1.030-1.034; LDL4, 1.035-1.040; LDL5, 1.041-1.047; LDL6, 1.048-1.057; LDL7, 1.058-1.066 g/mL), and cholesterol concentration was determined in each subfraction. Large-buoyant LDL was defined as LDL1 + LDL2, intermediate LDL as LDL3 + LDL4, and small-dense LDL as LDL5 + LDL6 + LDL7.

Intra- and interassay variability was less than 5% [29]. Each run contained the 2 plasma samples analyzed for each individual patient to exclude interrun differences.

The LDL subfractions were represented by the cholesterol concentration in each LDL subfraction. Furthermore, the LDL subfraction profile was expressed in relative terms by dividing the cholesterol concentration of each individual LDL subfraction by the total LDL-C (LDL1-LDL7).

Cholesterol and triglyceride levels were measured enzymatically using an automated clinical chemistry analyzer (Epos, Eppendorf, Hamburg, Germany). High-density lipoprotein cholesterol was determined after precipitation of apolipoprotein B–containing lipoproteins by dextran sulfate and magnesium acetate. Low-density lipoprotein cholesterol was determined by preparative ultracentrifugation (18 hours, d = 1.006 g/mL, 50 000 rpm, 4°C, Beckmann Ti 50.4 rotor). In the supernatant, VLDL-C and VLDL triglycerides were measured. In the infranatant (containing HDL and LDL),

Table 1
Preapheresis concentrations (mg/dL) of lipoproteins during placebo/during ezetimibe treatment and placebo

	Preapheresis during placebo treatment	Preapheresis during ezetimibe treatment	Change (%)[a]
Total cholesterol	222 (227 ± 32)	201 (200 ± 38)	−10.3** (−11.7 ± 12.6)
LDL-C	152 (156 ± 30)	132 (133 ± 28)	−13.5** (−13.5 ± 17.8)
Large-buoyant LDL-C	25.5 (27.0 ± 12.1)	22.8 (22.1 ± 11.1)	−17.3* (−18.9 ± 28.9)
Intermediate LDL-C	75.4 (77.0 ± 16.2)	61.2 (64.8 ± 18.5)	−17.1** (−14.4 ± 22.3)
Small-dense LDL-C	47.2 (52.0 ± 15.2)	46.9 (45.8 ± 11.0)	−6.5 (−9.2 ± 18.9), NS
HDL-C	48 (49 ± 13)	53 (51 ± 12)	2.50 (+2.8 ± 11.9), NS
VLDL-C	18 (21 ± 14)	15 (16 ± 12)	−31.4* (−14.5 ± 59.3)
Triglycerides	123 (135 ± 68)	99 (116 ± 61)	−14.6 (−8.4 ± 34.5), NS
VLDL triglycerides	94 (111 ± 75)	63 (90 ± 69)	−23.2* (−8.1 ± 65.4)

All values are given as median (mean ± SD). NS indicates nonsignificant.
[a] Refers to the change (%) of lipoproteins and of cholesterol in LDL subfractions during ezetimibe treatment compared with placebo; Wilcoxon test.
** $P < .01$.
* $P < .05$.

cholesterol was measured, then LDL was precipitated. Low-density lipoprotein cholesterol was calculated by subtraction of cholesterol in the supernatant (HDL-C) from total cholesterol in the infranatant.

All variables were tested for gaussian distribution by the Shapiro-Wilks and Kolmogorov-Smirnov tests. As not all variables were normally distributed, nonparametric tests were used for comparison (Wilcoxon matched-pairs test). Thus, the presented data are preferentially described by the median (besides mean ± SD). Statistical evaluation was performed using the Statistical Package of Social Sciences software (SPSS for Windows 11.5, SPSS Chicago, IL).

3. Results

At the beginning of both treatment periods, patients had similar median preapheresis cholesterol (214 vs 227 mg/dL), LDL-C (147 vs 155 mg/dL), HDL-C (46 vs 51 mg/dL), VLDL-C (18 vs 20 mg/dL), triglyceride (112 vs 132 mg/dL), and VLDL triglyceride (82 vs 110 mg/dL) concentrations (before placebo vs before ezetimibe: $P > .05$ for all variables, Wilcoxon test).

As reported previously, the addition of ezetimibe to concomitant intensive lipid lowering (LDL apheresis + statins) resulted in a lower median preapheresis LDL-C concentration (132 mg/dL) compared with placebo (152 mg/dL), which corresponds to a further reduction by 13.5% ($P < .01$) (Table 1). Additional ezetimibe also further decreased the median cholesterol (−10.3%), VLDL-C (-31.4%), and VLDL triglyceride concentration (−23.2%), whereas there was no significant change of HDL-C and triglycerides (Table 1).

During ezetimibe treatment compared with placebo, the median cholesterol concentration was further reduced in large-buoyant (−17.3%, $P < .05$), intermediate (−17.1%, $P < .01$), and small-dense LDL subfractions (−6.5%, $P = .07$) (Table 1). With respect to the individual LDL subfractions, ezetimibe significantly reduced cholesterol in subfractions LDL1 to LDL5, whereas in subfractions LDL6 and LDL7, cholesterol concentrations were similar during active and during placebo treatment (Figs. 1 and 2).

In relative terms, the reduction of cholesterol under ezetimibe compared with placebo was more pronounced in larger LDL subfractions (mean ± SD: −20% ± 28%, −17% ± 32%, −14% ± 25%, −13% ± 27%, −11% ± 21%, −7% ± 21%, −4% ± 19% for LDL1-LDL7, respectively; median values are given in Fig. 2). Although there was a slight increase of the relative amount of LDL6 and LDL7 during ezetimibe treatment compared with placebo, overall, the LDL subtype profile was not signifi-

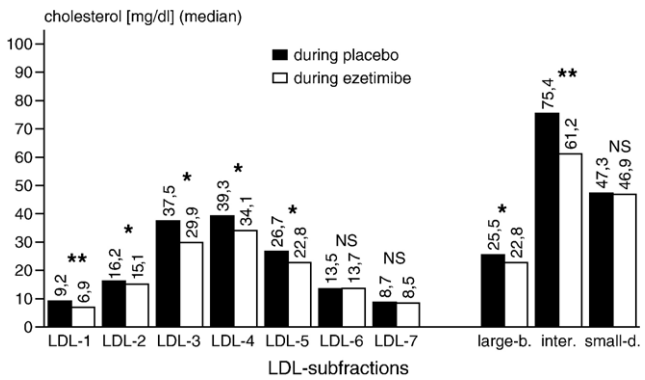

Fig. 1. Cholesterol concentration (mg/dL) in each LDL subfraction during ezetimibe treatment compared with placebo (medians). *$P < .05$, **$P < .01$; Wilcoxon test. NS indicates nonsignificant.

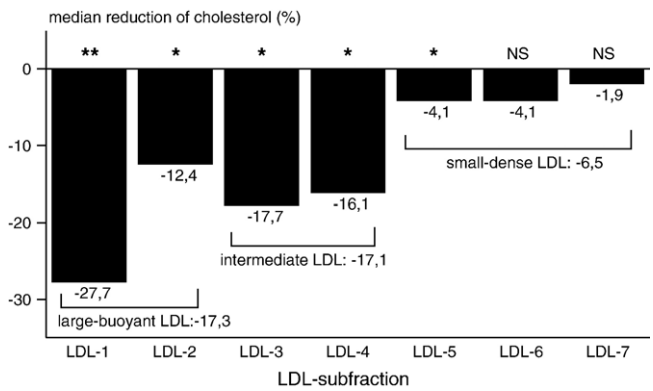

Fig. 2. Reduction (%) of cholesterol in each LDL subfraction under ezetimibe compared with placebo (medians). *$P < .05$, ** $P < .01$; Wilcoxon test.

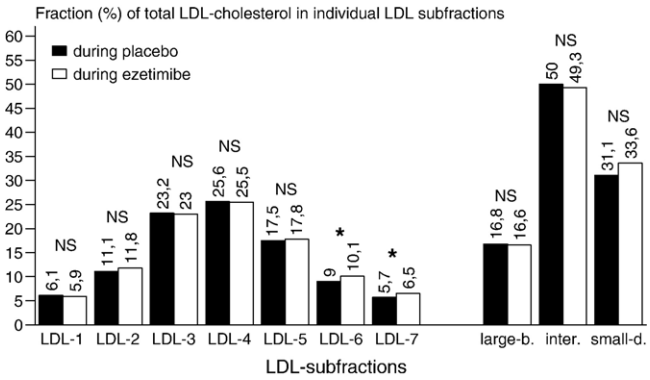

Fig. 3. Low-density lipoprotein subfraction profile during ezetimibe treatment and during placebo (medians). The LDL subtype profile was obtained by dividing the cholesterol concentration in each individual LDL subfraction by the total LDL-C (corresponding to the sum of the cholesterol content in all 7 LDL subfractions). Thus, the LDL subtypes shown are expressed as percentage from total LDL-C. *$P < .05$, Wilcoxon test.

cantly changed (large-buoyant LDL, 16.3% ± 7.2% vs 17.2% ± 6.4%; intermediate LDL, 48.2% ± 5.2% vs 49.3% ± 4.5%; and small-dense LDL, 35.5% ± 10.0% vs 33.5% ± 8.0% during ezetimibe treatment vs placebo) (Fig. 3).

The results described above were unchanged after exclusion of the 2 patients with combined hyperlipidemia (data not shown). The observed changes in LDL subtype distribution are not biased by altered dietary behavior, as we found no differences in body mass index (27.3 vs 27.2 kg/m^2) and in the intake of total energy, fat, carbohydrate, and protein as well as in the alcohol or cholesterol consumption under ezetimibe compared with placebo [27].

4. Discussion

Overall, the addition of ezetimibe to statins in patients treated by regular LDL apheresis because of severe LDL hypercholesterolemia and coronary heart disease did not significantly change the LDL subtype profile. However, with respect to the individual LDL subfractions we observed a more pronounced reduction of cholesterol in large-buoyant and intermediate LDL than in small-dense LDL.

As all LDL subfractions contribute to cardiovascular risk and large-buoyant [13] as well as small-dense LDL [6-12] are known to be more atherogenic than intermediate LDL subfractions, this result may be of clinical importance.

A comparison of our results to other studies is limited as there is only one study that investigated the influence of ezetimibe on LDL subtypes using a different methodology (gradient gel electrophoresis) [17]. The authors compared ezetimibe vs placebo and ezetimibe combined with fenofibrate vs fenofibrate in patients with mixed hyperlipoproteinemia and predominant small-dense LDL, thus, in patients metabolically different from those in our study. In this study, ezetimibe compared with placebo improved the LDL size in only 22% of the patients, whereas the majority (69%) showed no change or even a shift to a more dense LDL pattern (9%) [17]. Moreover, the addition of ezetimibe to fenofibrate did not further improve the LDL size compared with fenofibrate alone. These results suggest that overall ezetimibe may reduce LDL subtypes rather equally [17]. Thus, the minor differences between our study and the above-cited study [17] probably relate to differences in methodology, co-medication, and underlying metabolic disease. For patients with isolated LDL hypercholesterolemia, no data are available.

The finding that the cholesterol reduction during ezetimibe treatment was greater in larger compared with dense LDL subfractions is difficult to interpret with respect to its clinical significance. Keeping in mind that large-buoyant LDLs have been shown to be independently associated with further cardiovascular events in patients with prior myocardial infarction and moderate LDL hypercholesterolemia [13,14], our finding might be beneficial for this special patient group. However, there is ongoing dispute if the study results of Campos et al can be generalized [12,16] as there is a large body of evidence from other studies [6-12] that small-dense LDL are much more important concerning LDL subtype associated atherogenicity. This is further substantiated by the long-term follow-up of the Quebec Cardiovascular Study [12] indicating that small-dense LDL, and not large-buoyant LDL, is an independent cardiovascular risk factor.

Ezetimibe did not reduce cholesterol in LDL subfractions LDL6 and LDL7. As it is well known that changes in triglycerides induced by diet or lipid-lowering drugs are a major predictor of a reduction of small-dense LDL [16,30], this result may be related to the lack of a significant triglyceride reduction in our patients. Thus, in hypertriglyceridemic patients or in patients with combined hyperlipidemia, ezetimibe may have a different effect on LDL subtypes. The observation of Farnier et al [17] who showed that only a fraction of patients with mixed hyperlipidemia (22%) had an improvement in the LDL size may be related to this predictor. Our patients were divided according to their change in triglycerides under ezetimibe (reduction ≤10% vs >10%) to further evaluate if any change in triglycerides might have influenced our findings; however, there was no difference between both groups with respect to the influence of ezetimibe on the LDL subfraction profile (data not shown). Moreover, the 2 patients with severe combined hyperlipoproteinemia also showed a change of the LDL subfraction profile similar to that seen in the whole group. On the other hand, the impact of ezetimibe on triglycerides is rather small (−6% [20,25] to −15% [17,19,23]), and, thus, a much greater number of patients would be needed to reveal any association between the ezetimibe-induced change in triglycerides and its influence on the LDL subfraction profile.

Overall, ezetimibe seems to show an effect on LDL subfractions that is similar to that seen under statins if the comparison is done with a similar patient group [31,32]. However, it was also shown that statins have no uniform effect on the LDL subfraction profile, which may relate to

the fact that the studies differed in statin dose, study population, and underlying metabolic disease including presence or absence of insulin resistance. The effect of ezetimibe on small-dense LDL is also similar to that seen during bile acid–sequestering resins [33], which were shown only to reduce "light" (corresponding to large-buoyant) and not small-dense LDL subfractions. Thus, it could be assumed that any LDL-C–lowering approach, which is achieved by an increased LDL receptor activity, may have a similar effect on LDL subtype distribution.

It also remains unknown how ezetimibe acts on crucial elements involved in the production of small-dense LDL such as VLDL1 precursors, cholesterol ester transfer protein (CETP), and hepatic lipase activity. Ezetimibe decreases the hepatic cholesterol pool, resulting in an increase of LDL receptor activity and thus an increased LDL catabolism. Intermediate-dense LDL may be reduced in particular because they show the best binding profile to the LDL receptor [5]. By this mechanism, the greater reduction of intermediate compared with small-dense LDL subfractions may be explained. Large-buoyant LDL on the other hand may be reduced because there is less production of triglyceride-rich lipoproteins and/or because larger LDLs are more efficiently converted to intermediate LDL. The clarification of the involved pathways would require tracer studies.

In summary, the addition of ezetimibe to intensive lipid lowering (statins + LDL apheresis) in patients with severe hypercholesterolemia and coronary heart disease further reduced cholesterol in nearly all LDL subfractions, and there was a more pronounced reduction of larger compared with more dense LDL subfractions.

References

[1] Chapman MJ, Goldstein S, Lagrange D, et al. A density gradient ultracentrifugal procedure for the isolation of the major lipoprotein classes from human serum. J Lipid Res 1981;22:339-58.

[2] Krauss RM, Burke DJ. Identification of multiple subclasses of plasma low density lipoproteins in normal humans. J Lipid Res 1982; 23:97-104.

[3] Tribble DL, Holl LG, Wood PD, et al. Variations in oxidative susceptibility among 6 low density lipoprotein subfractions of differing density and particle size. Atherosclerosis 1992;93: 189-99.

[4] La Belle M, Krauss RM. Differences in carbohydrate content of low density lipoproteins associated with low density lipoprotein subclass patterns. J Lipid Res 1990;31:1577-88.

[5] Nigon F, Lesnik P, Rouis M, et al. Discrete subspecies of human low density lipoproteins are heterogeneous in their interaction with the cellular LDL receptor. J Lipid Res 1991;32:1741-53.

[6] Austin MA, Breslow JL, Hennekens CH, et al. Low-density lipoprotein subclass patterns and risk of myocardial infarction. JAMA 1988;260:1917-21.

[7] Watts GF, Mandalia S, Brunt JN, et al. Independent associations between plasma lipoprotein subfraction levels and the course of coronary artery disease in the St Thomas' Atherosclerosis Regression Study (STARS). Metabolism 1993;42:1461-7.

[8] Austin MA, King M, Vranizan KM, et al. Atherogenic lipoprotein phenotype: a proposed genetic marker for coronary heart disease risk. Circulation 1990;82:495-506.

[9] Lamarche B, Tchernof A, Moorjani S, et al. Small, dense low-density lipoprotein particles as a predictor of the risk of ischemic heart disease in men. Circulation 1997;95:69-75.

[10] Griffin BA, Freeman DJ, Tait GW, 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.

[11] Vakkilainen J, Steiner G, Ansquer J-C, et al. Relationships between LDL lipoprotein particle size, plasma lipoproteins, and progression of coronary artery disease. Circulation 2003;107:1733-7.

[12] St-Pierre AC, Cantin B, Dagenais GR, Mauriege P, 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 2001;25:1-7.

[13] Campos H, Moye LA, Glasser SP, et al. Low-density lipoprotein size, pravastatin treatment, and coronary events. JAMA 2005;286: 1468-74.

[14] Sacks FM, Campos H. Low density lipoprotein size and cardiovascular disease: a reappraisal. J Clin Endocrinol Metab 2003;88: 4525-32.

[15] Chapman MJ, Guerin M, Bruckert E. Atherogenic, dense low-density lipoproteins. Pathophysiology and new therapeutic approaches. Eur Heart J 1998;19(Suppl A):A24-A30.

[16] Berneis K, Rizzo M. LDL size: does it matter? Swiss Med Wkly 2004;134:720-4.

[17] Farnier M, Freeman MW, Macdonell G, et al. Efficacy and safety of the coadministration of ezetimibe with fenofibrate in patients with mixed hyperlipidaemia. Eur J Heart 2005;26:897-905.

[18] Kerzner B, Corbelli J, Sharp S, et al. Ezetimibe Study Group. Efficacy and safety of ezetimibe coadministered with lovastatin in primary hypercholesterolemia. Am J Cardiol 2003;91:418-24.

[19] Ballantyne CM, Houri J, Notarbartolo A, et al. Ezetimibe Study Group. Effect of ezetimibe coadministered with atorvastatin in 628 patients with primary hypercholesterolemia: a prospective, randomized, double-blind trial. Circulation 2003;107:2409-15.

[20] Davidson MH, McGarry T, Bettis R, et al. Ezetimibe coadministered with simvastatin in patients with primary hypercholesterolemia. J Am Coll Cardiol 2002;40:2125-34.

[21] Gagne C, Gaudet D, Bruckert E. Ezetimibe Study Group. Efficacy and safety of ezetimibe coadministered with atorvastatin or simvastatin in patients with homozygous familial hypercholesterolemia. Circulation 2002;105:2469-75.

[22] Gagne C, Bays HE, Weiss SR, et al. Ezetimibe Study Group. Efficacy and safety of ezetimibe added to ongoing statin therapy for treatment of patients with primary hypercholesterolemia. Am J Cardiol 2002; 90:1084-91.

[23] Goldberg AC, Sapre A, Liu J, et al. Ezetimibe Study Group. Efficacy and safety of ezetimibe coadministered with simvastatin in patients with primary hypercholesterolemia: a randomized, double-blind, placebo-controlled trial. Mayo Clin Proc 2004;79:620-9.

[24] Melani L, Mills R, Hassman D, et al. Ezetimibe Study Group. Efficacy and safety of ezetimibe coadministered with pravastatin in patients with primary hypercholesterolemia: a prospective, randomized, double-blind trial. Eur Heart J 2003;24:717-28.

[25] Dujovne CA, Ettinger MP, McNeer JF, et al. Ezetimibe Study Group. Efficacy and safety of a potent new selective cholesterol absorption inhibitor, ezetimibe, in patients with primary hypercholesterolemia. Am J Cardiol 2002;90:1092-7.

[26] Pearson TA, Denke MA, McBride PE, et al. A community-based, randomized trial of ezetimibe added to statin therapy to attain NCEP ATP III goals for LDL cholesterol in hypercholesterolemic patients: the ezetimibe add-on to statin for effectiveness (EASE) trial. Mayo Clin Proc 2005;80:587-95.

[27] Geiss HC, Otto C, Hund-Wissner E, et al. Effects of ezetimibe on plasma lipoproteins in severely hypercholesterolemic patients treated with regular LDL-apheresis and statins. Atherosclerosis 2005;180: 107-12.

[28] Geiss HC, Bremer S, Barrett PH, et al. In vivo metabolism of LDL subfractions in patients with heterozygous familial hypercholesterolemia on statin therapy: rebound analysis of LDL subfractions after LDL apheresis. J Lipid Res 2004;45:1459-67.

[29] Schamberger BM, Geiss HC, Ritter MM, et al. Influence of LDL apheresis on LDL subtypes in patients with coronary heart disease and severe hyperlipoproteinemia. J Lipid Res 2000;41:727-33.

[30] Mc Namara JR, Jenner JL, Li Z, et al. Change in LDL particle size is associated with change in plasma triglyceride concentration. Arterioscler Thromb 1992;12:1284-90.

[31] Geiss HC, Otto C, Schwandt P, et al. Effect of atorvastatin on low-density lipoprotein subtypes in patients with different forms of hyperlipoproteinemia and control subjects. Metabolism 2001; 50:983-8.

[32] Geiss HC, Schwandt P, Parhofer KG. Influence of simvastatin on LDL-subtypes in patients with heterozygous familial hypercholesterolemia and in patients with diabetes mellitus and mixed hyperlipoproteinemia. Exp Clin Endocrinol Diabetes 2002;110:182-7.

[33] Homma Y, Kobayashi T, Yamaguchi H, et al. Specific reduction of plasma large, light low-density lipoprotein by a bile acid sequestering resin, cholebine (MCI-196) in type II hyperlipoproteinemia. Atherosclerosis 1997;129:241-8.