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Simvastatin and Ezetimibe in Addition to Nonpharmacological Risk Factor Modification for Achieving New Low-Density Lipoprotein Cholesterol Targets

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Ezetimibe · Cholesterol absorption inhibition · Statin · Cardiac rehabilitation · Secondary prevention · Coronary artery disease · Coronary heart disease

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Abstract

Background: Though guidelines emphasize low-density lipoprotein cholesterol (LDL-C) lowering as an essential strategy for cardiovascular risk reduction, achieving target levels may be difficult.

Patients and Methods: The authors conducted a prospective, controlled, open-label trial examining the effectiveness and safety of high-dose fluvastatin or a standard dosage of simvastatin plus ezetimibe, both with an intensive guideline-oriented cardiac rehabilitation program, in achieving the new ATP III LDL-C targets in patients with proven coronary artery disease. 305 consecutive patients were enrolled in the study. Patients were divided into two groups: the simvastatin (40 mg/d) plus ezetimibe (10 mg/d) and the fluvastatin-only group (80 mg/d). Patients in both study groups received the treatment for 21 days in addition to nonpharmacological measures, including advanced physical, dietary, psychosocial, and educational activities.

Results: After 21 days of treatment, a significant reduction in LDL-C was found in both study groups as compared to the initial values, however, the reduction in LDL-C was significantly stronger in the simvastatin plus ezetimibe group: simvastatin plus ezetimibe treatment decreased LDL-C to a mean level of 57.7 ± 1.7 mg/ml, while fluvastatin achieved a reduction to 84.1 ± 2.4 mg/ml ($p < 0.001$). In the simvastatin plus ezetimibe group, 95% of the patients reached the target level of LDL-C < 100 mg/dl. This percentage was significantly higher than in patients treated with fluvastatin alone (75%; $p < 0.001$). The greater effectiveness of simvastatin plus ezetimibe was more impressive when considering the optional goal of LDL-C < 70 mg/dl (75% vs. 32%, respectively; $p < 0.001$). There was no difference in occurrence of adverse events between both groups.

Conclusion: Simvastatin 40 mg/d plus ezetimibe 10 mg/d, on the background of a guideline-oriented standardized intensive cardiac rehabilitation program, can reach 95% effectiveness in achieving challenging goals (LDL < 100 mg/dl) using lipid-lowering medication in patients at high cardiovascular risk.

Schlüsselwörter:
Ezetimib · Inhibition der Cholesterinabsorption · Statin · Kardiale Rehabilitation · Sekundäre Prävention · Koronare Herzkrankheit

Simvastatin und Ezetimib zusätzlich zur Lebensstiländerung im Rahmen einer Rehabilitationsmaßnahme zur Erzielung der neuen LDL-Cholesterin-Richtwerte

Zusammenfassung

Hintergrund: Obwohl Leitlinien die LDL-C-(„low-density lipoprotein cholesterol"-)Reduktion als wesentliche Strategie für die kardiovaskuläre Risikoreduktion hervorheben, ist es oft schwierig, die Zielwerte zu erreichen.

Patienten und Methodik: Die Autoren überprüften in einer prospektiv-offenen, kontrollierten Untersuchung die Effektivität und Sicherheit einer hochdosierten Fluvastatintherapie und einer standarddosierten Simvastatintherapie plus Ezetimib. Beide Therapien erfolgten während eines intensiven leitlinienorientierten kardialen Rehabilitationsprogramms zum Erreichen der neuen ATP-III-LDL-C-Zielwerte bei Patienten mit einer erwiesenen koronaren Herzerkrankung. 305 Patienten wurden konsekutiv in die Studie eingeschlossen. Die Patienten wurden zwei Gruppen zugeteilt: Eine Gruppe erhielt eine Tagesdosis von 40 mg Simvastatin plus 10 mg Ezetimib, die andere Gruppe eine alleinige Tagesdosis von 80 mg Fluvastatin. Alle Patienten wurden über 21 Tage im Rahmen eines leitlinienorientierten, standardisierten und intensivierten kardialen Rehabilitationsprogramms behandelt.

Ergebnisse: Nach 21 Tagen zeigte sich im Vergleich zu den Ausgangswerten eine signifikante Reduktion des LDL-C in beiden Gruppen mit jedoch signifikant stärker ausgeprägtem Effekt in der Gruppe mit Simvastatin plus Ezetimib. Die Kombination erniedrigte LDL-C auf im Mittel 57,7 ± 1,7 mg/ml, während

Fluvastatin im Mittel 84,1 ± 2,4 mg/ml erreichte (p < 0,001). In der mit Simvastatin plus Ezetimib behandelten Gruppe erreichten 95% der Patienten ein Ziel-LDL-C < 100 mg/dl. Dieser Anteil war signifikant größer als bei den allein mit Fluvastatin behandelten Patienten (75%; p < 0,001). Die höhere Effektivität von Simvastatin plus Ezetimib gegenüber Fluvastatin war eindrücklicher im Erreichen des optionalen Ziel-LDL-C < 70 mg/dl (75% vs. 32%; p < 0,001). Ein Unterschied im Auftreten von Nebenwirkungen zwischen beiden Gruppen bestand nicht.

Schlussfolgerung: Unter einer lipidsenkenden Therapie mit einer Tagesdosis von 40 mg Simvastatin plus 10 mg Ezetimib bei begleitend leitlinienorientiertem, standardisiertem und intensiviertem kardialem Rehabilitationsprogramm bei Patienten mit hohem kardiovaskulärem Risiko lassen sich LDL-Zielwerte < 100 mg/dl mit 95%iger Effektivität erzielen.

Introduction

Strict implementation of therapeutic lifestyle changes and efficient pharmacotherapy is a cornerstone of secondary prevention in coronary artery disease. Patients with established coronary artery disease remain at high risk till initiating an effective secondary prevention strategy. Guidelines by expert panels emphasize low-density lipoprotein cholesterol (LDL-C) lowering as an essential strategy for cardiovascular risk reduction. According to implications of recent clinical trials from the 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 (ATP III), further reduction of the target LDL-C levels to < 70 mg/dl was defined as therapeutic option especially for patients at very high risk [1].

Ezetimibe (MSD SHARP & DOHME, Haar, Germany) is an FDA-approved (2003) medication that selectively inhibits the intestinal absorption of cholesterol and related phytosterols. It is the first member of a novel class of selective cholesterol absorption inhibitors. Ezetimibe is binding to the Niemann-Pick C1-like 1 (NPC1L1) protein which has been identified as an important transporter molecule responsible for cholesterol uptake in the brush border membrane of enterocytes [2, 3]. Ezetimibe reduces total cholesterol, LDL-C, apolipoprotein B and triglycerides and increases high-density lipoprotein (HDL) in patients with hypercholesterolemia [4–6]. It does not increase the incidence of myopathy or rhabdomyolysis when co-administered with statins [4–7].

We designed our study as an open-label, controlled, prospective trial examining the effectiveness and safety of two lipid-lowering therapies: simvastatin 40 mg/d plus ezetimibe 10 mg/d therapy (preformed combination tablet) or fluvastatin 80 mg/d tablet in the setting of an intensive, guideline-oriented cardiac rehabilitation program (with disciplinary dietary, physical, psychosocial, and educational measures) in achieving the new LDL-C levels. Our intention was not to design the study as comprehensive and detailed "head-to-head" comparison between simvastatin plus ezetimibe and fluvastatin. The primary efficacy endpoint was the change in LDL-C plasma levels between simvastatin plus ezetimibe and fluvastatin alone to the end of the 21-day treatment. The secondary efficacy endpoint was the percentage of patients who achieved the actual ATP III treatment goal for lipid management in high-risk patients.

Patients and Methods

All patients with established coronary artery disease entering the cardiac rehabilitation program at our institution and not having exclusion criteria were assigned, in the period from 10/2004 to 02/2005, to fluvastatin therapy and, in the period from 09/2005 to 02/2006, to simvastatin plus ezetimibe therapy, irrespective of their initial LDL-C level or intake of another lipid-lowering agent at the time of presentation. The exclusion criteria for the study were: known hypersensitivity to statins or previous documented side effects under statin therapy, hepatic injury (defined as hepatic transaminase levels exceeding the upper normal limit by a factor of 3), or systemic corticosteroid therapy. 305 consecutive patients (240 men and 65 women, mean age 62.9 ± 0.6 years) with established coronary artery disease were enrolled in the study. 55% of patients had a history of percutaneous coronary intervention (PCI), 45% of coronary artery bypass grafting (CABG), 51% of myocardial infarction, and 24% were diabetics. No patient from our study population had a history of hypo- or hyperthyroidism. All patients provided written informed consent before initiating the study medication. 76% of patients were already pretreated with a statin, however, with another type or another dosage of the drug. These statins were substituted with the study medication. The study population represents a wide spectrum of patients treated in a standard cardiology and rehabilitation care facility.

The standardized cardiac rehabilitation program at our institution consists of physical, psychosocial, and educational activities. Patients were integrated into 25-, 50-, and 75-W workload groups and

Table 1. Baseline characteristics of simvastatin plus ezetimibe and fluvastatin groups. Data are expressed as mean ± SEM (standard error of the mean). ACE: angiotensin-converting enzyme; BMI: body mass index; CABG: coronary artery bypass grafting; CAD: coronary artery disease; NS: not significant; PCI: percutaneous coronary intervention.

Tabelle 1. Ausgangscharakteristika der Gruppen mit Simvastatin plus Ezetimib und Fluvastatin. Die Daten sind als Mittelwert ± SEM (mittlere Standardabweichung) angegeben. ACE: Angiotensinkonversionsenzym; BMI: Body-Mass-Index; CABG: koronare Bypassoperation; CAD: koronare Herzkrankheit; NS: nicht signifikant; PCI: perkutane Koronarintervention.

Parameter	Simvastatin + ezetimibe (n = 176)	Fluvastatin (n = 129)	p-value
Age (years), mean ± SEM	62.5 ± 0.8	63.4 ± 0.9	NS
Sex (%)			NS
• Male	80	77	
• Female	20	23	
BMI (kg/m^2), mean ± SEM	28 ± 0.4	28.1 ± 0.4	NS
CAD (%)			NS
• 1-vessel disease	26	24	
• 2-vessel disease	20	23	
• 3-vessel disease	54	53	
Without significant stenosis	0	1	
CABG (%)	41	50	NS
PCI (%)	56	53	NS
Diabetes (%)	22	26	NS
Smoking (%)	49	38	NS
Hypertension (%)	97	89	< 0.05
Obesity (%)	51	51	NS
Family history of premature CAD (%)	71	70	NS
Comedication (%)			
• β-blocker	98	94	NS
• Calcium antagonists	2	10	< 0.01
• ACE inhibitors	98	90	< 0.01
• Antiarrhythmics	6	7	NS
• Oral antidiabetic	12	18	NS
• Insulin	5	11	< 0.05
• Digoxin	0	2	NS
• Aspirin	98	94	NS
• Clopidogrel	45	33	< 0.05

took part in individualized ergometric training, coordination training, terrain training, exercises in water basins, and swimming. The psychosocial part of the cardiac rehabilitation program implied reintegration and social issues, practice of relaxation techniques, stress management, and smoking cessation strategies. Educational aspects consisted of lectures on making healthy food choices, combating obesity, diabetes and hyperlipoproteinemia prevention, and problem-oriented topics on hypertension and peripheral artery disease.

The diet given to our patients was prepared according to recommendations of the European Heart Network summarized in material on Food, Nutrition and Cardiovascular Disease Prevention in the European Region. Total cholesterol intake was < 200 mg/d, saturated fat content < 10% and trans fat content < 2% of dietary energy; fruit and vegetables supply was > 400 mg/d.

Patients were divided into two groups: the simvastatin plus ezetimibe (SIMVA+E) and the fluvastatin-only group (FLUVA). In the SIMVA+E group, simvastatin 40 mg/d and ezetimibe 10 mg/d were given. In the FLUVA group, fluvastatin 80 mg/d was administered. We considered the FLUVA group more a control group, which should represent the conventional approach compared to modern combination therapy with ezetimibe. Patients in both study groups received treatment for 21 days. Blood sampling for entry lipid analysis – LDL-C, total cholesterol, high-density lipoprotein cholesterol (HDL-C), and triglycerides – was done at the 1st day of hospitalization. Lipid analysis was performed as direct homogeneous assay (Olympus AU640, Olympus America, Inc., Melville, NY, USA). The lipid analysis was repeated on day 21 after treatment initiation. Along with lipid analysis, plasma glucose, serum aspartate transaminase (AST) and creatine kinase (CK) were measured.

Statistics

Data are expressed as mean ± SEM (standard error of the mean). Numerical variables were tested by t-test and Mann-Whitney rank sum test, respectively, depending on the type of tested distribution. The difference in proportions of categorical data was tested by χ^2- and Fisher's exact test. p-values < 0.05 were considered statistically significant. All statistical tests were performed using SPSS 13.0 statistical software.

Results

A total of 305 patients were enrolled into the study, 176 to the SIMVA+E group and 129 to the FLUVA group. Demographics and baseline characteristics of both groups were similar (Table 1). Lipid parameters at entry were also very well comparable (Table 2). We carried out an explicit analysis of former hypolipidemic treatment of patients in both study groups. Corresponding frequencies in SIMVA+E and FLUVA groups were: no previous hypolipidemic treatment in 24% and 25%, treatment with atorvastatin in 27% and 25%, fluvastatin in 25% and 26%, pravastatin in 2% and 2%, simvastatin in 21% and 20%, fibrates in 1% and 2%, niacin in 0% and 0%, respectively. There were no significant differences between both groups concerning previous hypolipidemic treatment.

Primary Endpoint

After 21 days of treatment, we found a significant reduction in LDL-C in both study groups in comparison to the initial values, however, the reduction in LDL-C was significantly stronger in the SIMVA+E group: simvastatin plus ezetimibe treatment decreased LDL-C to a mean level of 57.7 ± 1.7 mg/ml, while fluvastatin reduced it to 84.1 ± 2.4 mg/ml ($p < 0.001$; Table 2). There was a mean decrease ΔLDL-C = –42.6% ± 1.8% in the SIMVA+E group and ΔLDL-C = –12.4% ± 2.7% in the FLUVA group ($p < 0.001$; Table 2).

Secondary Endpoint

In the SIMVA+E group, 95% of patients reached the target level of LDL-C < 100 mg/dl. This percentage was significantly higher than in patients treated with fluvastatin alone (75%; $p < 0.001$; Figure 1). This effect was more noticeable when taking an LDL-C level < 70 mg/dl as a target (75% effectiveness in SIMVA+E vs. 32% in the FLUVA group; $p < 0.001$; Figure 1).

Safety

During the 21-day treatment we did not observe any relevant change in transaminase levels (mean AST after treatment was 25.5 ± 1.2 IU/l in the SIMVA+E and 23.7 ± 1.4 IU/l in the FLUVA group, respectively; $p = 0.3$). CK levels did not change either (75.2 ± 4.2 IU/l and 72.9 ± 4.8 IU/l, respectively; $p = 0.6$). Fasting blood glucose levels at inclusion were not different (113.7 ± 4.5 mg/dl in the SIMVA+E, 113.3 ± 3.4 mg/dl in the FLUVA group; not significant [NS]) and did not change significantly at the end of the study (109.3 ± 3.2 mg/dl in the SIMVA+E, 106.7 ± 3.3 mg/dl in the FLUVA group; NS). One patient in the FLUVA group indicated an inclination to depression and another patient in the FLUVA group experienced meteorism.

Table 2. Baseline lipid profile, lipid profile after 21 days of treatment, and percentage change in lipid profile after 21 days of treatment in both study groups. Data are expressed as mean ± SEM (standard error of the mean). HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol.

Tabelle 2. Ausgangslipidprofil, Lipidprofil nach 21-tägiger Therapie und prozentuale Änderung des Lipidprofils beider Studiengruppen nach 21-tägiger Therapie. Die Daten sind als Mittelwert ± SEM (mittlere Standardabweichung) angegeben. HDL-C: „high-density lipoprotein cholesterol"; LDL-C: „low-density lipoprotein cholesterol".

Parameter	Simvastatin + ezetimibe (n = 176)	Fluvastatin (n = 129)	p-value
Baseline lipid profile			
• Total cholesterol (mg/dl)	173.3 ± 3.1	167.1 ± 3.6	NS
• LDL-C (mg/dl)	100.4 ± 2.5	95.7 ± 2.8	NS
• HDL-C (mg/dl)	42.6 ± 0.8	43.1 ± 1.2	NS
• Triglycerides (mg/dl)	151.9 ± 5.7	143.7 ± 8.2	NS
Lipid profile after 21 days of treatment			
• Total cholesterol (mg/dl)	125.4 ± 2.2	151.1 ± 3.1	< 0.001
• LDL-C (mg/dl)	57.7 ± 1.7	84.1 ± 2.4	< 0.001
• HDL-C (mg/dl)	45.2 ± 0.8	42.2 ± 1.1	< 0.05
• Triglycerides (mg/dl)	113.9 ± 4.1	124.0 ± 4.8	< 0.05
Percentage change after 21 days of treatment			
• Total cholesterol (%)	–27.6 ± 1.3	–9.6 ± 1.7	< 0.001
• LDL-C (%)	–42.6 ± 1.8	–12.4 ± 2.7	< 0.001
• HDL-C (%)	–6.1 ± 1.6	+2.1 ± 2.1	< 0.05
• Triglycerides (%)	–25.0 ± 1.9	–13.7 ± 6.5	< 0.05

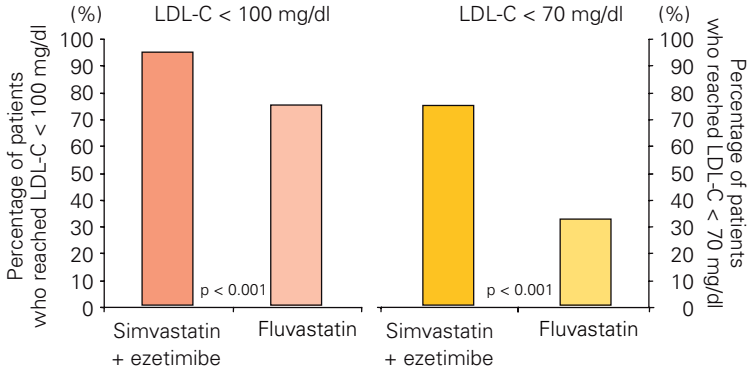

Figure 1. Percentage of patients who reached LDL-C < 100 mg/dl and LDL-C < 70 mg/dl.

Abbildung 1. Anteil der Patienten, die Zielwerte LDL-C < 100 mg/dl und LDL-C < 70 mg/dl erreichten.

Discussion

The study demonstrates impressive 95% effectiveness of simvastatin in combination with ezetimibe in achieving LDL-C < 100 mg/dl and 75% effectiveness in achieving LDL-C < 70 mg/dl in patients with established cardiovascular disease undergoing a guideline-oriented cardiac rehabilitation program.

The Euro Heart Survey Program of risk factor management and use of prophylactic drug therapies in patients with established coronary heart disease showed that only 50% of patients receiving hypolipidemic treatment reached the goal of 110 mg/dl, despite increased frequency of statin treatment [8]. Although higher doses of statins are more effective in lipid lowering, the risk of side effects appears to be dose-dependent [9]. Combination treatment with effect on different sites of cholesterol pathways may lead to additive clinical benefits. The addition of ezetimibe to a statin facilitates a further 14–20% reduction in LDL-C [10].

In the Lipid Treatment Assessment Project [11], 62% of statin-treated patients did not reach their es-

tablished LDL-C goal. Many factors may contribute to low goal attainment, including the lack of adequate dose titration, insufficient gain in LDL-C reduction with doubling of dose, perception of safety issues with use of higher doses, and insufficient LDL-C reductions at maximal dose with some statin brands. Concerning the spectrum of our patients, where 55% of patients had a history of PCI, 45% of CABG, and 51% of myocardial infarction, we did not see the possibility to enforce a placebo-controlled design.

The recent periodic meta-analysis made by the Cholesterol Treatment Trialists' Collaboration Group showed a 12% proportional reduction in all-cause mortality per 39 mg/dl (= 1 mmol/l) reduction in LDL-C (rate ratio [RR] 0.88, 95% confidence interval [CI] 0.84–0.91; p = 0.0001). This reflected a 19% reduction in coronary mortality (RR 0.81, 95% CI 0.76–0.85; p = 0.0001), and nonsignificant reductions in noncoronary vascular mortality and nonvascular mortality. There were corresponding reductions in myocardial infarction or coronary death, in the need for coronary revascularization, in fatal or nonfatal stroke. The statin therapy can reduce the 5-year incidence of major coronary events, coronary revascularization, and stroke by about 21% per 38.6 mg/dl reduction in LDL-C [12]. Similar data were published from a meta-analysis of 18 statin trials showing 15% reduction in overall mortality, 24% in coronary mortality, 27% reduction of incidence of nonfatal myocardial infarction, and 24% of stroke per 39 mg/dl [13].

In our study population, there was an absolute reduction in LDL-C of 42.7 ± 2.3 mg/dl in the SIMVA+E group and 11.6 ± 2.7 mg/dl in the FLUVA group. It is important to take into consideration, that this was achieved after previous statin therapy (76% patients had lipid-modifying therapy already at entering the study). This emphasizes the impact of intensive behavioral and lifestyle measures in further reducing cardiovascular risk even in patients with ongoing long-term pharmacotherapy and our data further advocate the approach of a strict individually adapted cardiac rehabilitation.

In a recently published trial on ezetimibe added to statin therapy to attain NCEP ATP III goals for LDL-C in hypercholesterolemic patients (EASE), simvastatin and ezetimibe were effective to reach ATP III LDL-C goals according to different risk classes in 71% of patients [14]. This is in concordance with our data, where the effect of the same combination pharmacotherapy was potentiated by a strict implementation of therapeutic lifestyle changes. This further underscores the potential of behavioral interventions. Low rates of adverse events and good tolerability of statin and ezetimibe have already been shown in previous trials oriented on safety issues [15].

Very recent data from the Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression Trial (ENHANCE) [16] recalled important clinical questions. Despite a 16.5% net benefit of simvastatin 80 mg and ezetimibe 10 mg in decreasing LDL-C in comparison to simvastatin 80 mg monotherapy, ezetimibe failed to show any change in the primary outcome measure defined as mean carotid artery intima-media thickness change after 24-month therapy. The lack of vascular benefit of ezetimibe in spite of incremental LDL-C reduction is still discussed. Possible explanations are referred: lipid-independent effects, especially anti-inflammatory action and improvement of endothelial function favoring statin therapy, too low-risk study population, and the inability of the intima-media thickness measurement to accurately reflect changes in atherosclerotic burden. In the light of these disappointing results in surrogate outcome, we are looking very much forward to the results of IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE IT), which is focusing on clinical outcomes (death due to any cardiovascular events, nonfatal coronary events, and nonfatal strokes) of simvastatin/ezetimibe combination therapy, which are expected in 2012.

One of the promising features of ezetimibe is that it is not increasing the risk of statin-induced myopathy, a complication possibly linked to coenzyme Q10 depletion during statin therapy. Ezetimibe has been shown not to affect coenzyme Q10 levels [7].

Interesting long-term (24-month follow-up) data about risk factor modification during a 3-week outpatient rehabilitation program were published recently. 31% of 327 patients participating in an outpatient guideline-oriented cardiac rehabilitation program achieved LDL < 100 mg/dl and this effect remained constant for 24 months after rehabilitation program completion [17]. Whether the inpatient and outpatient settings for cardiac rehabilitation program are equivalent regarding the prognostic impact, requires direct comparison and further evaluation.

The diet given to our patients is standardized according to recommendations of the European Heart Network summarized in material on Food, Nutrition and Cardiovascular Disease Prevention in the European Region. It has already been shown that this type of nutritional intervention could account for an LDL-C decrease of 12% [18]. On the other hand, the effect of aerobic exercise manifests mainly in changes in triglycerides and HDL – it decreases triglyceride levels and increases HDL. Exercise without dietary changes decreases LDL-C only moderately by about 5% [19]. With an optimal diet and exercise regimen it is possible to lower total cholesterol and LDL-C by 10–15%.

Conclusion

In an environment of maximized behavioral risk factor modification, lipid-lowering medication using simvastatin 40 mg/d combined with ezetimibe 10 mg/d can reach NCEP/ATP target level of LDL-C < 100 mg/dl in 95% of patients with established coronary artery disease. Simvastatin 40 mg/d and ezetimibe 10 mg/d in the setting of guideline-oriented therapeutic lifestyle modifications represent a very effective and safe therapeutic intervention to achieve challenging goals in hypolipidemic treatment in patients at high cardiovascular risk.

Limitations

This is not a randomized trial and therefore has all shortcomings of a nonrandomized design. The main limitation of this study is that we cannot account for the individual effect of the nonpharmacological regimen and that of the study medication on LDL-C reduction. Furthermore, because of ethical issues a washout period for statin pretreatment is lacking in the study design. Therefore, it cannot be concluded to what extent the study drug effect has been influenced by the pretreatment. The baseline LDL-C level was relatively low in both groups, probably because of the high incidence of ongoing lipid-lowering therapies at inclusion, yet in spite of this combination SIMVA+E medication significantly reduced the LDL-C level compared to the FLUVA group. Also a selection effect caused by the increased motivation of participants and the not evaluated effect on other modifying factors (e.g., body mass index, blood pressure, heart rate) could cause study bias.

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