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CLINICAL TRIAL

The effect of simvastatin, ezetimibe and their combination on the lipid profile, arterial stiffness and inflammatory markers

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Abstract
Objective Arterial stiffness and highly sensitive C-reactive protein (hsCRP) serum level predict the risk for cardiovascular events. The most commonly used drugs for lowering cholesterol levels, the statins, also have anti-inflammatory effects and can decrease arterial stiffness. Ezetimibe is the first drug of a new class of cholesterol absorption inhibitors in common use and, to date, its effect on arterial stiffness has not yet been studied. The aim of this study was to compare the effect of simvastatin and ezetimibe, both singly and in combination, on arterial stiffness and hsCRP serum concentration in hypercholesterolemic patients.
Methods Forty hypercholesterolemic patients were studied. Group1 comprised previously untreated patients, who received simvastatin at doses of 40 mg/day during the study; group 2 comprised patients previously treated with simvastatin at 40 mg/day, who received simvastatin at 80 mg/day during the study; group 3 consisted of patients previously untreated, who received ezetimibe at doses of 10 mg/day during the study; group 4 comprised patients previously treated with simvastatin at 40 mg/day, who received simvastatin at 40 mg/day and ezetimibe at 10 mg/day during the study. Arterial stiffness expressed as the Augmentation Index (AIx) (assessed by pulse wave analysis), the lipid profile and the hsCRP level were measured at baseline and after 3 months of treatment.
Results The reduction in low-density lipoprotein (LDL) after treatment was significantly greater in groups 1 and 4 (39.9 and 35.7%) than in groups 2 and 3 (17.7 and 16.9%; $p=0.005$). The AIx decreased significantly only in group 1 patients, from 30.2±8.3% before treatment to 21.6±6.5% after treatment ($p<0.001$). Changes in hsCRP paralleled the changes in AIx, with a significant decrease in patients in group 1 only, from 2.8±2.5 mg/L before treatment to 1.6±1.5 mg/L after treatment ($p=0.016$).
Conclusion Ezetimibe as a monotherapy had no effect on arterial stiffness or hsCRP, while the administration of simvastatin at 40 mg per day improved arterial stiffness and CRP. However, increasing the dose of simvastatin or administering ezetimibe in combination with simvastatin had no beneficial effects on arterial stiffness.

Keywords Arterial stiffness · CRP · Ezetimibe · Simvastatin

Introduction

Lipid-lowering therapy has a proven survival benefit in patients with hypercholesterolemia by preventing both primary and secondary cardiovascular events [1]. The mechanisms of these beneficial effects can be, in part, explained by the reduction in the levels of serum low-density lipoprotein (LDL) [2–6]. Among the non-lipid mechanisms possibly involved are reduced inflammation, decreased thrombogenicity, plaque stabilization and reversal of endothelial dysfunction [7, 8].

Several classes of drugs are known to be capable of altering lipid metabolism, including statins, fibric acid

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derivatives, bile acid sequestrants, nicotinic acid, probucol and cholesterol absorption inhibitors, including ezetimibe. These classes of drugs differ with respect to their mechanisms of action and their potency to decrease serum lipid levels. Statins are currently the most commonly used drugs with the most powerful effect of lowering LDL cholesterol [7]. They also possess anti-inflammatory properties [9–11] and have a beneficial effect on arterial stiffness [12–14]. However, two major adverse events are related to statin therapy – hepatic dysfunction and muscle toxicity. Ezetimibe is the first drug of a new class of cholesterol absorption inhibitors that impair dietary and biliary cholesterol absorption at the brush border of the intestine without affecting the absorption of triglycerides or fat-soluble vitamins [15]. Ezetimibe is effective as monotherapy or as an adjunctive therapy in combination with statins [16–20], and it has been shown to be well tolerated in clinical trials, with no demonstrable adverse systemic events [16–20]. The co-administration of ezetimibe and statins has been shown to reduce C-reactive protein (CRP) levels, however ezetimibe as a single therapy has no significant effect on CRP [21]. Endothelial function, as assessed by forearm blood flow, has been improved by a combination of ezetimibe and atorvastatin but not by ezetimibe as a single drug [22, 23].

The effects of ezetimibe on arterial stiffness have not yet been investigated. The aim of the present study, therefore, was to assess the effect of statin therapy at low and high doses in comparison to that of ezetimibe administered as a single drug or in a combination with statin on highly sensitive CRP and arterial stiffness.

Methods

Patients

Patients with baseline LDL levels >120 mg/dL or LDL levels >100 mg/dl while on statin therapy were included. The exclusion criteria were a recent (less than 3 months) myocardial infarction or cerebrovascular event, uncontrolled hypertension (HTN), uncontrolled heart failure, any cardiac arrhythmia, chronic or acute inflammatory conditions, newly diagnosed or uncontrolled diabetes mellitus (hemoglobin A1c > 7%), serum triglycerides >250 mg/dL, abnormal liver function tests or creatine kinase levels exceeding the upper normal value. The medical regimen of the patients was not changed throughout the study period. The protocol was approved by the local Helsinki Committee for Experiments on Humans.

Experimental design

There were four treatment groups:

- Patients who had not been treated with cholesterol-lowering therapy during the 3 months preceding the study were assigned either to the group receiving simvastatin at doses of 40 mg/day (Simovil, MSD Israel) or to the group receiving ezetimibe at 10 mg/day (Ezetrol, MSD Israel). Patients with a history of an adverse reaction to simvastatin were also assigned to receive ezetimibe at 10 mg/day. Patients who had not been previously treated with statins were assigned to receive simvastatin 40 mg/day.
- Patients already on a simvastatin regimen of 40 mg/day for more than 3 months who had not achieved the target LDL level of <100 mg/dL were assigned to the group receiving either simvastatin at 80 mg/day (group 3) or the group receiving combined therapy consisting of simvastatin at 40 mg/day and ezetimibe at 10 g/day (group 4). Patients in these two groups of the study were not included in the simvastatin 40 mg/day group.

After enrolment, both the patients and the doctors knew the medication regimen prescribed each patient.

Patients were subjected to a complete physical examination and laboratory analyses twice during the study: at baseline and after 3 months of treatment. All analyses were performed in the morning after an overnight fast and 12 h after the last medication dose. The full physical examination included weight, height and blood pressure measurements. Blood was drawn for the measurement of hemoglobin, hemoglobin A1c, creatinine, liver function tests, hsCRP and the lipid profile, including total cholesterol high-density lipoprotein (HDL) and triglycerides (TG). the LDL concentration was calculated. The study was designed to ensure that ten patients in each group would complete the 3-month study protocol.

Pulse wave analysis

Assessment of arterial stiffness was performed at baseline and following 3 months of treatment by means of a noninvasive technique using the commercially available SphygmoCor System (AtCor Medical, Australia). All measurements were performed by one of the authors (S.E.) while the patient was in the recombinant position at room temperature (25°C). In brief, peripheral pressure waveforms were recorded from the radial artery at the wrist, using applanation tonometry with a high-fidelity micromanometer (Millar Instruments, Houston, Tex.). When 20 sequential waveforms were recorded, a validated 16–18 generalized

transfer function was applied to generate the corresponding central aortic pressure waveform. The Augmentation Index (AIx) and augmented pressure (AP) were derived by calculation, using the pulse wave analysis technique (Fig. 1) [24]. The merging point of the incident and reflected wave (the inflection point) was identified on the generated aortic pressure waveform. AP was calculated as the maximum systolic pressure minus the pressure at the inflection point. AIx was calculated as the AP divided by the pulse pressure and expressed as a percentage. Higher values of AIx indicated increased wave reflection from the periphery or earlier return of the reflected wave as a result of increased pulse wave velocity (attributable to increased arterial stiffness), and vice versa. Only high-quality recordings, defined as those with an in-device quality index >80% (as derived from an algorithm that includes average pulse height, pulse height variations, diastolic variations and the maximum rate of rise of the peripheral waveform), and the curves acceptable upon a visual inspection performed by one investigator were included in the analysis. All pulse wave measurements were taken in the same sitting position, in a quiet, temperature-controlled room (23±1°C), after a resting period of t least 15 min. All measurements of AIx and AP were performed and determined automatically by the SphygmoCor System software.

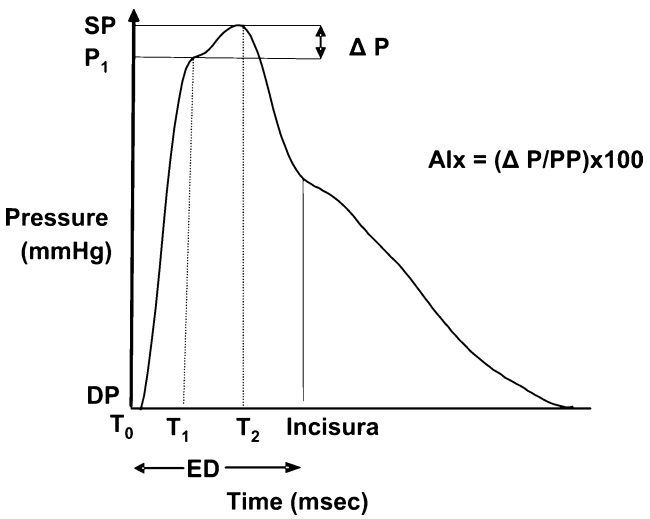

Fig. 1 Hemodynamic parameters derived by pulse wave analysis of the central aortic pressure wave. T_0 Time at the start of the waveform, T_1 duration from the start of the waveform to the first peak/shoulder (outgoing pressure wave), T_2 duration from the start of the waveform to the second peak/shoulder (reflected pressure wave), *ED* ejection duration, or duration from the start of the waveform to closure of the aortic valve (*incisura*), *SP* central aortic systolic pressure, *DP* central aortic diastolic pressure, P_1 height difference between the minimum pressure and the pressure at the first peak/shoulder (T_1). Augmentation (*P*) difference between maximal pressure (central aortic systolic pressure) and pressure at the first peak/shoulder (P_1 height), *PP* pulse pressure, *AIx* augmentation index

Statistical analysis

The sample size of ten patients in each group (total 40 patients) was determined in order to achieve 90% power and was based on the following assumption related to the *expected AIx evaluation* in the study population: a mean difference between the groups of at least 25% and a standard deviation of 15% within each group. However, *the actual results* in the study population were different, as will be detailed in the results and, accordingly, the real power of the study with regard to the AIx was 85%. Statistical analysis was performed using the statistical software SPSS ver. 13 (SPSS, Chicago, Ill.). Parametric data were expressed as means ± standard deviations and compared by one-way ANOVA using the Bonferroni for Post Hoc analysis. Non-parametric data were compared using the Kolmogorov-Smirnov test. Differences between the results with a p value of less than 0.05were considered to be statistically significant.

Results

Forty three patients were included in the study. Three patients were excluded: two due to an infectious disease during the follow-up period (one patient in the simvastatin 40 mg/day group and one patient in the simvastatin+ ezetimibe group) and one patient (in the simvastatin 40 mg/day group) because his antihypertensive therapy was altered during the follow-up period. There were no other adverse events during the study.

The study group receiving ezetimibe at 10 mg/day included patients who had been treated in the past (more than 3 months prior to the commencement of this study) with statins and who had exhibited some adverse reaction(s) to this therapy. The adverse reactions included muscle pain without significant CPK elevation (six patients), rhabdomyolysis (one patient) and elevated liver enzymes (three patients).

Demographic and clinical characteristics of the patients are presented in Table 1. There were no significant differences in any of the baseline characteristics between the four treatment groups.

The effects of treatment on lipid profiles are summarized in Table 2 and Fig. 2. Patients in groups 1 (simvastatin, 40 mg/day) and 4 (simvastatin, 40 mg + ezetimibe) showed the most significant decrease in plasma LDL-cholesterol (p= 0.005). In group 1 patients, plasma LDL-cholesterol decreased from 159±11 mg/dL before treatment to 95± 12 mg/dL at the 3-month follow-up (40±4% reduction, p<

Table 1 Patients' demographic and clinical data (n=10 patients in each group)

	Simvastatin, 40 mg/day	Simvastatin, 80 mg/day	Ezetimibe, 10 mg/day	Simvastatin, 40 mg/day with ezetimibe, 10 mg/day
Age (years)	60±11	58±13	57±12	59±9
Sex (male/female)	7/3	8/2	8/2	6/4
Body mass index (kg/ m^2)	32±5	26±4	28±3	29±5
Systolic blood pressure (mm Hg)	124±9	128±8	125±12	130±11
Diastolic blood (mm Hg)	69±9	73±7	68±6	74±10
Cardio-cerebrovascular disease (%)	7 (70%)	9 (90%)	6 (60%)	8 (80%)
Diabetes mellitus (%)	1 (10%)	2 (20%)	1 (10%)	2 (20%)
Hypertension (%)	8 (80%)	7 (70%)	7 (70%)	9 (90%)
Smokers (%)	2 (20%)	3 (30%)	1 (10%)	3 (30%)
Concomitant medications (%):				
Aspirin	10 (100%)	9 (90%)	10 (100%)	10 (100%)
β-blockers	3 (30%)	4 (40%)	2 (20%)	3 (30%)
Calcium channels blockers	2 (20%)	1 (10%)	3 (30%)	2 (20%)
ACE inhibitors[a]/A-II receptor blockers	7 (70%)	5 (50%)	8 (80%)	7 (70%)
Diuretics	5 (50%)	6 (60%)	6 (60%)	5 (50%)

[a] ACE, Angiotension-converting enzyme

0.001), and in group 4 patients, it decreased from 133± 29 mg/dL to 83±23 mg/dL (36±17% reduction, p<0.001). Increasing the simvastatin dose from 40 mg to 80 mg/day (group 3) resulted in a mild and marginally significant decrease in plasma LDL-cholesterol (17±19% reduction, p=0.064; Table 2). Ezetimibe as monotherapy (group 2) resulted in a mild and significant decrease in plasma LDL-cholesterol by 18±13% (p=0.02; Table 2). Plasma HDL increased significantly by the end of the treatment in group 1 patients (simvastatin, 40 mg), from 49±12 mg/dL to 56.0±10.1 mg/dL (p=0.05). There was no change in plasma HDL in the other groups. Serum triglycerides levels remained unchanged at the end of treatment in all groups (Table 2).

Treatment with simvastatin at 40 mg/day (group1) resulted in a significant decrease in hsCRP, from 2.8±2.5 mg/L to 1.6±1.5 mg/L (p=0.016). No statistically significant changes in hsCRP concentrations were observed in the other study groups (Table 2). There was significant correlation between the changes in LDL and those in hsCRP (r^2=0.003, p= 0.787). The results of the hsCRP analysis are summarized in Table 2 and Fig. 3.

The effects of treatment on peripheral and central hemodynamics are presented in Table 3. Treatment with 40 mg simvastatin daily (group 1) resulted in a significant decrease in AIx, from 30.2±8.3% before treatment to 21.6± 6.5%, (p<0.001. Treatment had no effect on any hemodynamic parameter in the other treatment groups. As shown in Fig. 4, the mean changes (deltas) in AIx in the simvastatin 40 mg group was significantly different from those found for the other three groups of the study: −29.2±10.1 in the simvastatin 40 mg group versus +4.9±21.4 in the simvastatin 80 mg group versus +7.9±4.3 in the ezetimibe 10 mg group and 2.5±28.5 in the simvastatin 40 mg + ezetimibe 10 mg group (p=0.038, p=0.10 and p=0.09 for each of the comparisons, respectively). According to these parameters, the statistical power of the study was 85%. There was no significant correlation between the changes in LDL and

Table 2 Lipid profile and highly sensitive C-reactive protein (hsCRP) levels in the different study groups (n=10 patients in each group)

	Simvastatin, 40 mg/day		Simvastatin, 80 mg/day		Ezetimibe, 10 mg/day		Simvastatin, 40 mg/day with ezetimibe, 10 mg/day	
	Baseline	3 months	Baseline	3 months	Baseline	3 months	Baseline	3 months
LDL (mg/dL)	159±10.9	95.3±11.8*	106.6±8.3**	88.1±17.5*	153.4±33.6	123.8±20.8	132.6±28.9	82.7±23.5*
HDL (mg/dL)	48.7±11.8	56.0±10.1*	46±12	48.1±11.5	63.7±17.8	61.3±13.4	54.3±13.1	52.4±12.5
TG (mg/dL)	130.1±37.3	118.6±34.7	104.8±37.8	92.5±41.5	149±77.8	110.4±70.4	136.2±59.1	108±46.9
hsCRP (mg/L)	2.8±2.5	1.6±1.5*	1.98±2.2	1.2±0.8	2.4±1.2	2.7±2.2	2.1±1.8	1.57±1.2

*p<0.05 significant for comparison within a given group.
**p<0.05 significant for comparison with the baseline at the other groups.

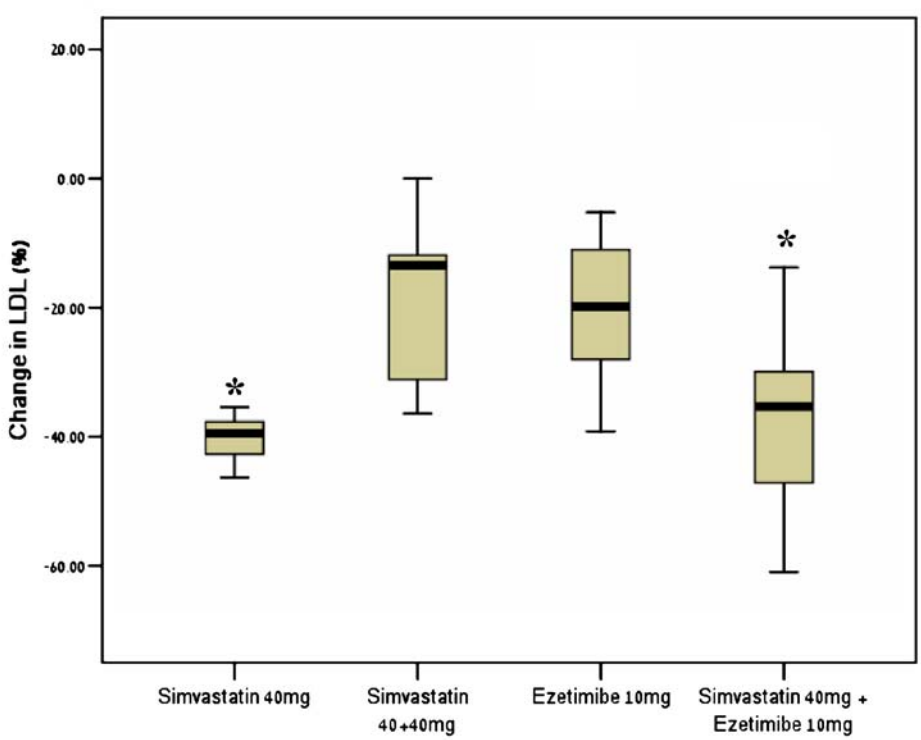

Fig. 2 Changes in LDL (%) in the different study groups (n=10 patents in each group). *p<0.05 compared to the groups receiving simvastatin at 80 mg/day and ezetimibe (one-way ANOVA; Bonferroni test applied for Post Hoc analysis)

* P<0.05 compared to the rest of the study groups (one way ANOVA using Bonferroni for Post Hoc analysis)

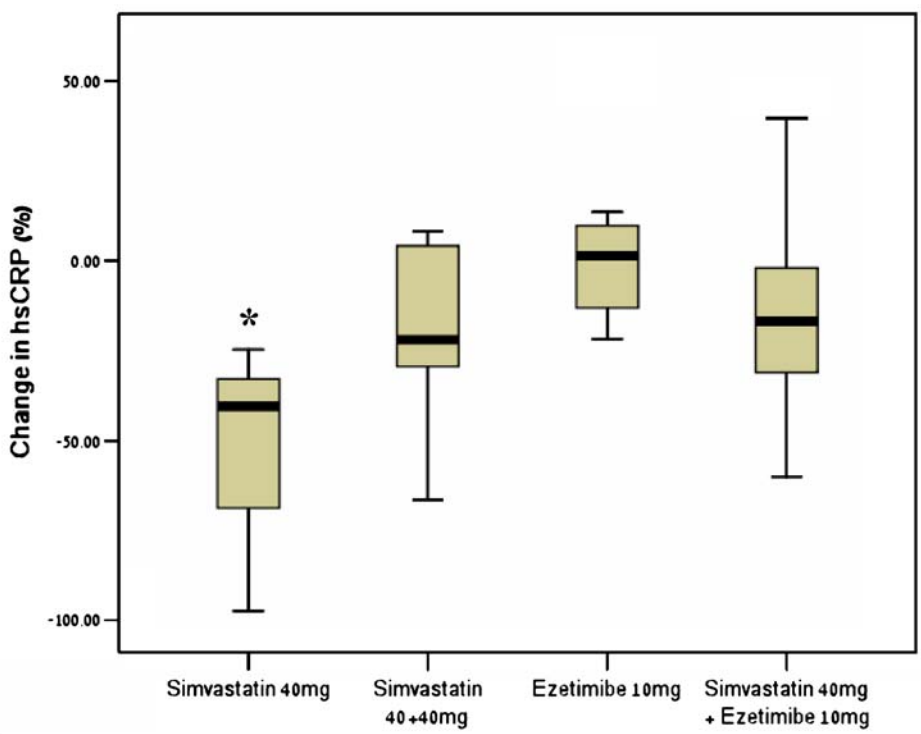

Fig. 3 Changes in highly sensitive C-reactive protein (CRP, %) concentration in the patients of the four study groups (n=10 I patients n each group). *p<0.05 compared to the rest of the study groups (one-way ANOVA using Bonferroni for Post Hoc analysis)

* P<0.05 compared to the rest of the study groups (one way ANOVA using Bonferroni for Post Hoc analysis)

Table 3 Hemodynamic and pulse wave analysis in the different study groups (n=10 patients in each group)

Hemodynamic and pulse wave parameters[a]	Simvastatin, 40 mg/day		Simvastatin, 80 mg/day		Ezetimibe, 10 mg/day		Simvastatin, 40 mg/day with ezetimibe, 10 mg/day	
	Baseline	3 months	Baseline	3 months	Baseline	3 months	Baseline	3 months
Peripheral SBP (mmHg)	125±8	123±9	129±10	128±11	126±9	128±8	124±11	123±9
Peripheral DBP (mmHg)	69±7	70±10	72±11	71±9	71±8	70±8	72±9	71±8
Central SBP (mmHg)	119±9	110±7	118±8	114±9	121±8	123±9	113±10	114±7
Central DBP (mmHg)	70±8	71±9	73±10	72±10	71±8	72±7	73±8	71±9
Heart rate (beat/minute)	69±6	68±5	69±8	67±6	70±7	68±9	66±10	64±9
AIx (mmHg)	14.8±4.1	8.4±2.6*	11.7±5.8	11.3±5.3	15.5±4.7	17.9±5.3	12.4±3.3	14.1±4.3
AIx (%)	30.2±8.3	21.6±6.5*	26.1±12.9	27.1±12.6	31.1±9.55	35.12±10.4	31.1±8.34	29.3±10.1

*p<0.05 significant for comparison within a given group.
[a] SBP, Systolic blood pressure; DBP, diastolic blood pressure; AIx, augmentation index

those in AIx (r^2=0.1, p=0.08), or between the changes in hsCRP and those in AIx (r^2=0.008, p=0.637).

Discussion

The present study evaluated the effects of administering a statin in two dosages (simvastatin 40 and 80 mg/day), the new cholesterol-lowering drug ezetimibe and the combination of simvastatin and ezetimibe on arterial stiffness and inflammation. Simvastatin administered at 40 mg/day exerted the maximal beneficial effect: it reduced LDL concentrations and decreased hsCRP and AIx. In accordance with results from other studies [25], a combination therapy of simvastatin+ ezetimibe was more potent in reducing LDL levels than a doubling of the simvastatin dose. Although the combination of simvastatin and ezetimibe had similar LDL lowering effects as the primary treatment with simvastatin 40 mg/day, only simvastatin 40 mg had a beneficial effect on hsCRP and arterial stiffness.

During recent years, inflammation, and CRP as one of its main markers, has emerged as one of the major factors in the initiation and progression of atherosclerotic lesions and plaque disruption [26]. It has been shown that statin therapy

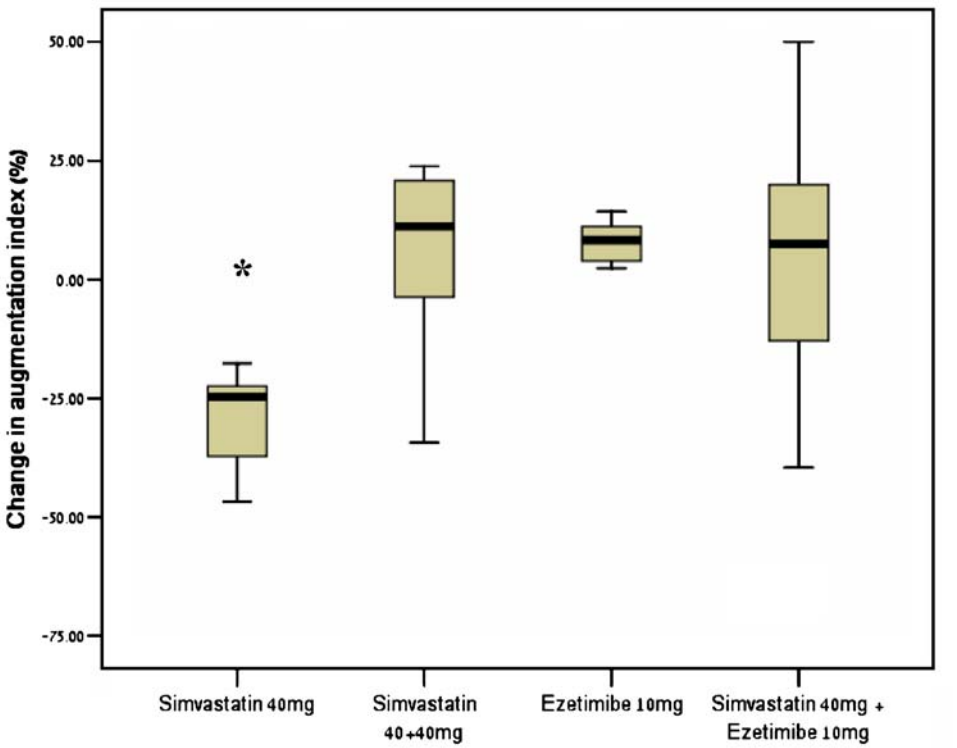

Fig. 4 Changes in the augmentation index (%) in the different study groups (n=10 patients in each group). *p<0.05 compared to the rest of the study groups (one-way ANOVA using Bonferroni for Post Hoc analysis)

* P<0.05 compared to the rest of the study groups (one way ANOVA using Bonferroni for Post Hoc analysis)

is associated with a better clinical outcome when levels of the inflammatory biomarker CRP are elevated and that statins are capable of lowering CRP levels in a manner almost completely independent of the level of LDL-cholesterol [27–31]. Ridker et al. showed that patients with ischemic heart disease who showed reduced CRP levels following statin therapy have better clinical outcomes than those with higher CRP levels, regardless of the levels of LDL-cholesterol [32]. In the present study, both the administration of simvastatin 40 mg alone and the combination of simvastatin and ezetimibe reduced LDL levels, but reduced CRP levels were observed only in the former group, which is in agreement with the literature.

The effect of ezetimibe on CRP in combination with statin therapy and as a single therapy was investigated by Sager et al. and Ballantyne et al. [21, 33], both of whom found that the combination of ezetimibe with statin therapy brought about a further decrease in LDL and CRP. However, ezetimibe as a single therapy had no significant beneficial effect on CRP [21, 33]. In accordance with these findings, we also found that the maximal anti-inflammatory effect occurred in patients treated with simvastatin, 40 mg/day. Ezetimibe administration as a single therapy or as added on to therapy with simvastatin at 40 mg/day did not have a statistically significant effect on CRP values. However, within the frame of the present experimental protocol, the differences in the reduction of hsCRP levels in response to combined simvastatin+ezetimibe therapy did not reach statistical significance. We suggest that this discrepancy could be explained by an insufficient number of patients within each group, by the differences in the treatment regimens, or both.

Augmentation pressure, which reflects the pulsatile component of blood pressure and, consequently, arterial stiffness, is a well-known risk factor for cardiovascular disease and outcome [34–38]. AIx, determined invasively and non-invasively, has been shown to predict coronary artery disease (CAD) [37, 39]. Vasodilating drugs, such as ACE inhibitors, Angiotensin II (A-II) antagonists and calcium-channel blockers may affect wave reflections and AIx [38, 40, 41]. The Conduit Artery Function Evaluation (CAFÉ) study, a substudy of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), examined the impact of two different blood pressure-lowering regimens (atenolol-thiazide-based versus amlodipine-perindopril-based therapy) on derived central aortic pressures and hemodynamics in 2199 patients [38]. Central pulse pressure was an independent risk factor for composite outcome of total cardiovascular events/procedures and the development of renal impairment [38]. In order to avoid the anti-hypertensive drugs effect on AIx in our study, care was taken to maintain the doses unchanged throughout the follow-up period.

Statins, in addition to their cholesterol-lowering and anti-inflammatory properties, have been shown to exert a significant beneficial effect on arterial stiffness [42–45]. This was reported to be associated with an increase in endothelial NO synthase [46, 47]. Hydrophilic and lipophilic statins may influence vascular smooth muscle cell accumulation and collagen production, irrespective of their cholesterol-lowering effect [48–52]. A significant reduction in arterial stiffness, decreased proliferation and increased apoptosis were observed in human vascular smooth muscle cells from patients treated with lipophilic statins, but not in cells from those treated with hydrophilic statins [48–52]. In accordance with these data, in our study lipophilic simvastatin exerted the most prominent effect on arterial stiffness. The effect was significant in patients treated with 40 mg/day simvastatin, while doubling the dose to 80 mg/day did not improve the outcome. It should be noted that the baseline LDL concentrations were significantly higher in the simvastatin 40 mg/day group than in the simvastatin 80 mg/day group. Even though there was no correlation between the effect on LDL and the effects on AIx and hsCRP, it can not be excluded that the beneficial effects of simvastatin 40 mg – which were achieved in the simvastatin 80 mg – are due to different mechanisms at the baseline LDL concentrations.

To the best of our knowledge, no study has yet evaluated the effect of ezetimibe on arterial stiffness. With the exception of the expectant lipid-lowering effect, especially in combination with simvastatin, ezetimibe exerted no significant effects on arterial stiffness throughout the 3-month follow-up. These finding are in accordance with the results recently reported by Landmesser et al. [53]. In the latter study, 20 patients with chronic heart failure were randomized to either 4 weeks of simvastatin (10 mg/day) or 4 weeks of ezetimibe (10 mg/day) treatment. While simvastatin improved flow-dependent vascular dilatation and increased the number of functionally active endothelial progenitor cells, ezetimibe had no significant effect of any of these parameters [53].

It should be emphasized that the present study was aimed to address the two main *clinical conflicts* the physician faces daily regarding the use of statins or ezetimibe. The first question is which is the optimal drug to start with? The second question deals with patients who do not achieve the target LDL levels with the standard dose of statin: should the dose be doubled or should ezetimibe be added as a combined therapy? This study was not intended to compare a high dose of statins to a standard dose, or to compare combinational therapy to ezetimibe or statins at a standard dose alone. Taken together, the results of the present study can be summarized as follows:

In patients starting cholesterol-lowering therapy, simvastatin, as compared to ezetimibe, offers additional beneficial

effects with respect to reducing hsCRP serum levels and arterial stiffness.

In patients already receiving standard statin treatment, a combinational treatment of statins with ezetimibe may be preferable. The maximal pleiotropic effect exerted by statins can be achieved by the standard treatment, and any further elevation of in the dose will have no further significant effect with regards to hsCRP and arterial stiffness, whereas combination with ezetimibe will amplify the cholesterol-lowering effect.

The present study was performed on a limited number of participants. More clinical trials are needed to investigate the effect of different cholesterol-lowering therapeutic options on inflammation and arterial stiffness and to correlate their role in prevention of cardiovascular events.

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