Chapter 8

Effects of simvastatin besides nifedipine on left ventricular mass and intima media thickness in patients with hyperlipidemia and hypertension

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Submitted
ABSTRACT

Background:
The addition of statin treatment to antihypertensive treatment with calcium channel blockers treatment might have a synergistic effect on cardiovascular remodeling in patients with multiple risk factors.

Objective:
To determine the effects of simvastatin versus placebo besides nifedipine treatment on left ventricular mass and intima media thickness in patients with combined hypertension and mild hypercholesterolemia.

Methods:
A total of 100 patients were randomized to simvastatin or placebo and treated for 2 years after having been treated with open label long acting nifedipine 30 or 60 mg for 26 weeks. Echocardiographically determined left ventricular mass and diastolic function, B-mode ultrasound scanning of carotid and femoral artery wall thickness and 24 hour ambulatory blood pressure was performed at baseline and at the end of the study.

Results:
After 2 years of treatment, left ventricular mass was borderline significantly reduced by simvastatin treatment (-19 ± se 1.7 g/m²) compared to placebo (-14 ± se 1.7 g/m²) with P = 0.05. Changes in intima media thickness and blood pressure were not different between both groups. Cholesterol was significantly lowered in the simvastatin group compared to placebo.

Conclusion:
The addition of simvastatin compared to placebo to nifedipine treatment did not result in changes in cardiovascular structure, although cholesterol was significantly lowered by simvastatin compared to placebo in these with nifedipine treated hypertensive patients with mild hypercholesterolemia.

INTRODUCTION

When hyperlipidemia is associated with hypertension, the risk of major cardiovascular events rises dramatically. Both left ventricular hypertrophy and increased intima media thickness have been shown to be independent prognostic factors for cardiovascular morbidity and mortality. Most surrogate endpoint hypertension studies use left ventricular mass, while statin studies have often used intima media thickness, but not left ventricular mass as an endpoint.

Statin therapy has many effects. Besides the well known reducing effects on intima
Effects of simvastatin besides nifedipine

media thickness as shown in many randomized trials 5-8, statins have recently been shown to inhibit angiotensin II-mediated induction of transcription factors c-jun and c-fos9. This observation raises the possibility that statins may induce regression of left ventricular mass by blocking signaling pathways independent of cholesterol-lowering effects.

The possibility that calcium channel blockers exert an anti-atherosclerotic action that is at least partly independent of their blood pressure lowering effect is supported by evidence obtained from several experimental models of atherosclerosis 10; 11. In two trials, the VHAS and the INSIGHT, calcium channel blockers were compared to diuretics using B-mode ultrasound. It was shown that calcium channel blockers reduced intima media thickness more effectively than the diuretics 12,13. Little is known about the possibly synergistic effects of hypolipaemic statin and antihypertensive calcium channel blocker treatment in patients with combined hypertension and hypercholesterolemia.

The objective of the present study was to assess the two year effects of adding simvastatin versus placebo to nifedipine treatment on left ventricular mass and intima media thickness in patients with treated hypertension and mild hypercholesterolemia.

METHODS

Patients
Subjects were recruited from an ongoing open label trial, studying the 26 weeks effects of long acting nifedipine on left ventricular mass, diastolic function and intima media thickness in patients with combined previously untreated hypertension and mild hypercholesterolemia.

These patients were recruited from a population survey. In this survey systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured in sitting position after 5 min of rest using the right arm. Those with previously untreated hypertension (to be defined as four measurements of SBP between 160-220 mmHg and/or DBP between 95-115 mmHg derived from multiple measurements made on three occasions over a period of 4 weeks) were treated with long acting nifedipine 30 or 60 mg for 26 weeks. Patients were advised to follow a cholesterol lowering diet. After these 26 weeks patients, who had still hypercholesterolemia, were invited to enter this two year follow up trial, studying the additive effects of simvastatin versus placebo treatment in these patients. Exclusion criteria for the randomization to simvastatin or placebo were all forms of secondary hypertension (tested by history and physical examination), total cholesterol greater than 8 mmol/L, clinically significant heart failure or valvular heart disease with hemodynamic consequences; cardiac
arrhythmias, pacemaker and myocardial infarction within the last 6 months; concomitant disease of the liver (liver function test > twice the upper limit of normal), kidneys (creatinine > 160 µmol/l), angina pectoris, diabetes mellitus, use of antilipaemic drugs, alcohol or drug abuse, any therapy known to affect absorption and the inability to give consent to participate in the study.

**Treatment regimen**

As stated above patients had been treated with long acting nifedipine 30 mg or 60 mg for 26 weeks. They were advised to take a cholesterol-lowering diet. After 26 weeks, cholesterol levels were determined, and the included patient with total cholesterol between 5.0 and 8.0 mmol/l were randomized to simvastatin 20 mg or placebo. After 8 weeks the dose was doubled to 40 mg when total cholesterol remained ≥ 5.0 mmol/l or had fallen less than 1.5 mmol/l. Besides these visits, after 26, 39, 52, 69, 84 and 104 weeks of treatment, routine control visits for conventional blood pressure measurements, adverse events registration and drug distribution took place.

**Office blood pressure measurements**

At each visit, blood pressure was measured twice with at least 2 minutes interval in the sitting position. The arm, in which the higher blood pressure values were measured at the start of the study, was used for further measurements. The heart rate was taken immediately after the first blood pressure measurement in sitting position by counting the pulse for at least one minute.

**Ambulatory blood pressure monitoring**

Ambulatory blood pressure (ABP) was measured at baseline and after two years of treatment using the SpaceLabs 90207 equipment (SpaceLabs Inc. Redmond Washington, USA).

Ambulatory blood pressure was recorded every 30 minutes during daytime (7.00-22.59h) and every 60 minutes during nighttime (23.00-6.59h). A cuff-size suitable to the arm circumference was selected. Patients were instructed to keep the arm still at the time of measurement and to carry out normal activities during the 24 hours of measurement. Ambulatory recordings were performed only on working days, and the blood pressures were not displayed on the monitor. ABP-data were analyzed without data-editing using time-weighed means. At least 80% of readings must be successful, otherwise the measurement was repeated if possible.
Echocardiography

Echocardiographic examinations were recorded by the same sonographer in the course of the study. An Acuson 128XP/10 (Acuson Corp., Mountain View, California, USA) with a 2.5-4.0 MHz transducer was used. Left ventricular dimensions were measured in 2-D mode according to the Penn-Convention in the left lateral decubitus position. Three recordings were made of end diastolic left ventricular wall (LVPW), interventricular septum (IVS) and left ventricular end diastolic diameter (EDD). To estimate left ventricular mass the cube formula of Devereux and Reichek\textsuperscript{14} was used. The left ventricular mass index was calculated by dividing left ventricular mass by body surface area.

Diastolic filling abnormalities were measured by using pulsed Doppler echocardiography. Measurements were done in the standard apical four-chamber view, with the patient in the left decubitus position. The Doppler sampling volume was placed between the tips of the mitral valve leaflets to obtain maximal filling velocities. Three recordings were made at the end of expiration. Early peak (E-peak) and atrial peak (A-peak) filling velocities were measured and their ratio (E/A ratio) calculated.

B-mode ultrasound

At baseline and after 2 years of treatment, B-mode ultrasound imaging of the carotid and the femoral arterial walls was done. An Acuson 128 XP (Acuson Corp., Mountain View, California, USA), equipped with a 7.0 MHz L7384 linear array transducer, was used by two experienced and certified sonographers, who were unaware of the clinical data. The methods used to record and analyze B-mode ultrasound images have been described in detail before\textsuperscript{15}. In short, ten prespecified right and left carotid and femoral arterial wall segments were imaged. In the carotid artery, the arterial segment 1 cm proximal to the carotid dilatation (the common carotid artery), the arterial segment between the carotid dilation and carotid flow divider (carotid bulb) and a 1 cm long arterial segment distal to the flow divider (internal carotid artery) were measured. In the femoral artery, a 1 cm long arterial segment proximal to the femoral dilation (common femoral artery) and a 1 cm arterial segment distal to the femoral flow divider (superficial femoral artery) were measured. Of each arterial segment, 5-s real time image sequences were stored on S-VHS. B-mode ultrasound video images were analyzed off-line (S-VHS Panasonic NV-FS 100 HQ; VCR; Sony GVM-1400 QM multisync monitor; IDEN IVT-7p time base correctors, IPC 80486 personal computer equipped with DT2861 and DT2862 frame grabbers) by one reader. Image analysis software was developed in cooperation with Selzer et al\textsuperscript{16}. The IMT of the far wall was evaluated as the distance between the luminal-intimal interface.
and the medial-advential interface. Six carotid and four femoral IMT data were aggregated to a single IMT value for each subject. The mean of the maximum IMT of up to ten combined far walls was the primary endpoint of the study. The mean of the mean IMT and the mean of the minimum IMT of up to ten combined far walls were secondary endpoints. In case macrovascular lesions were obvious and IMT was not measurable, lesions were considered plaques. Also, when IMT exceeded 1.2 mm, lesions were considered plaques. Plaques were scored as a dichotomous variable in the 10 predefined arterial segments in both the near and far walls. From repeated measurement procedures, the measurement error of variation in the population studied was calculated as 0.04 mm for the primary, combined carotid and femoral far wall IMT endpoint.

Statistical analysis
All statistical analyses (SAS software package, Cary, North Carolina, USA) were done by an independent statistical center (Trial Coordination Center, University Hospital Groningen, The Netherlands). The primary endpoint for treatment efficacy was the change in left ventricular mass index. A subanalysis of the primary endpoint was performed to assess differences in treatment effect of simvastatin for patients with larger screening LVMI. In order to assess this, an analysis of covariance (ANCOVA) was performed with the change in LVMI from randomization to end of the study as dependent variable and the screening LVMI, medication and their interaction as independent variables. The secondary endpoints of the study were the change in mean maximal far wall IMT, the change in mean 24 hours ambulatory systolic and diastolic blood pressure and the change in E/A ratio. Data are expressed as means ± standard error of the mean (sem) or mean ± standard deviation (SD). Paired t-test or Wilcoxon sign-rank test was used to test for changes of IMT after treatment, as appropriate. Results are of the intention-to-treat type of analysis. Before the start of the study, power calculations were performed. An IMT difference of 0.12 mm was detectable (using a SD of 0.251 mm, which we found in the REGRESS study), with a power of 0.83 and an alpha of 0.05. Calculations were based on power calculations by de Groot et al. 17 and Salonen et al 18. To determine whether relations existed between left ventricular mass, maximum IMT, ambulatory blood pressures and their changes after treatment, Spearman correlations were used. All statistical tests were two-sided with a significance level of P < 0.05.
RESULTS

Patients
In the population survey 5107 inhabitants between 25 and 60 years of age had their blood pressure measured. After three serial blood pressure measurements a total of 228 persons without antihypertensive drug treatment had DBP \(\geq 95\) mmHg and 150 previously untreated persons had SBP \(\geq 160\) mmHg and were considered hypertensive. They were offered to have their cholesterol levels checked and get their blood pressure taken for a fourth time. Out of this remaining group, 131 patients gave written consent and were treated with long acting nifedipine, and advised to take a cholesterol lowering

### Table 1 Baseline characteristics of 100 randomized patients

<table>
<thead>
<tr>
<th></th>
<th>Simvastatin (n = 50)</th>
<th>Placebo (n = 50)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>52 ± 6</td>
<td>52 ± 7</td>
<td>0.71</td>
</tr>
<tr>
<td>Gender M/F</td>
<td>23/27</td>
<td>25/25</td>
<td>0.84</td>
</tr>
<tr>
<td>Body Mass Index (kg/m²)</td>
<td>28 ± 5</td>
<td>29 ± 4</td>
<td>0.53</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>143 ± 12 (172 ± 15)</td>
<td>145 ± 13 (173 ± 15)</td>
<td>0.68</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>88 ± 7 (100 ± 7)</td>
<td>88 ± 7 (100 ± 7)</td>
<td>0.60</td>
</tr>
<tr>
<td>Heart rate (beats per minute)</td>
<td>70 ± 11</td>
<td>68 ± 10</td>
<td>0.74</td>
</tr>
<tr>
<td>Smokers (%)</td>
<td>46</td>
<td>44</td>
<td>0.97</td>
</tr>
<tr>
<td>Total cholesterol (mmol/l)</td>
<td>6.4 ± 0.8</td>
<td>6.3 ± 0.8</td>
<td>0.80</td>
</tr>
<tr>
<td>HDL - cholesterol (mmol/l)</td>
<td>1.3 ± 0.3</td>
<td>1.3 ± 0.4</td>
<td>0.53</td>
</tr>
<tr>
<td>LDL - cholesterol (mmol/l)</td>
<td>4.2 ± 0.8</td>
<td>4.3 ± 0.7</td>
<td>0.36</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td>1.7 ± 0.9</td>
<td>1.6 ± 0.8</td>
<td>0.65</td>
</tr>
<tr>
<td>Glucose (mmol/l)</td>
<td>4.7 ± 0.6</td>
<td>4.7 ± 0.5</td>
<td>0.92</td>
</tr>
<tr>
<td>Creatinine (µmol/l)</td>
<td>82 ± 17</td>
<td>83 ± 12</td>
<td>0.80</td>
</tr>
<tr>
<td>Plaques (%)</td>
<td>56</td>
<td>54</td>
<td>0.57</td>
</tr>
</tbody>
</table>

Values are mean ± SD. DBP, diastolic blood pressure; SBP, systolic blood pressure; M, male; F, female; n = number; HDL, high density lipoprotein; LDL, low density lipoprotein.
diet. After 26 weeks of treatment, 116 patients were still on nifedipine treatment whereas 15 patients dropped out, mostly due to adverse events. From these 116 patients 100 met the inclusion criteria and were randomized to simvastatin versus placebo. The population characteristics at baseline are summarized in Table 1.

**Effect of treatment on blood pressure, heart rate and metabolic variables**
At baseline, 32 patients were treated with nifedipine 30 mg and 68 patients were treated with nifedipine 60 mg, equally divided over both groups. There was no difference between simvastatin compared to placebo beside nifedipine treatment on 24 hour ambulant systolic and diastolic blood pressure, as seen in table 2. Lipid profiles however, were significantly lowered in the simvastatin group compared to placebo. After two years of treatment total cholesterol was 4.6 mmol/l (SD 0.9) in

<table>
<thead>
<tr>
<th>Table 2 Blood pressure values at baseline and at the end of study</th>
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<tr>
<td><strong>24-hours ambulatory systolic blood pressure (SBP) in mmHg</strong></td>
</tr>
<tr>
<td>Simvastatin</td>
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<td>Randomisation 50</td>
</tr>
<tr>
<td>End of trial 46</td>
</tr>
<tr>
<td>Placebo</td>
</tr>
<tr>
<td>Randomisation 50</td>
</tr>
<tr>
<td>End of trial 44</td>
</tr>
<tr>
<td><strong>24-hours ambulatory diastolic blood pressure (DBP) in mmHg</strong></td>
</tr>
<tr>
<td>Simvastatin</td>
</tr>
<tr>
<td>Randomisation 50</td>
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<tr>
<td>End of trial 46</td>
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<tr>
<td>Placebo</td>
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<tr>
<td>Randomisation 50</td>
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<tr>
<td>End of trial 44</td>
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</table>

P-value, change in diastolic and systolic blood pressure simvastatin versus placebo
Effects of simvastatin besides nifedipine

Table 3 Left ventricular mass index and diastolic function

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Mean</th>
<th>SE</th>
<th>Median</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Left ventricular mass index in g/m²</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Simvastatin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Randomisation</td>
<td>50</td>
<td>91.7</td>
<td>2.6</td>
<td>90.1</td>
<td></td>
</tr>
<tr>
<td>End of trial</td>
<td>47</td>
<td>73.9</td>
<td>1.8</td>
<td>74.8</td>
<td></td>
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<tr>
<td>Placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Randomisation</td>
<td>50</td>
<td>88.5</td>
<td>2.7</td>
<td>84.1</td>
<td>0.0548</td>
</tr>
<tr>
<td>End of trial</td>
<td>44</td>
<td>72.4</td>
<td>2.0</td>
<td>71.3</td>
<td></td>
</tr>
<tr>
<td><strong>Diastolic function</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simvastatin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Randomisation</td>
<td>50</td>
<td>1.05</td>
<td>0.03</td>
<td>0.99</td>
<td></td>
</tr>
<tr>
<td>End of trial</td>
<td>46</td>
<td>1.09</td>
<td>0.02</td>
<td>1.12</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Randomisation</td>
<td>49</td>
<td>1.04</td>
<td>0.04</td>
<td>0.98</td>
<td></td>
</tr>
<tr>
<td>End of trial</td>
<td>40</td>
<td>1.16</td>
<td>0.05</td>
<td>1.14</td>
<td>0.4943</td>
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</table>

P-value, change in left ventricular mass index and diastolic function simvastatin versus placebo

the simvastatin group (change 1.76 ± SD 0.88), compared to 6.4 mmol/l (SD 0.9) in the placebo group (change –0.04 ± SD 0.80), with P < 0.0001.

**Effect of treatment on left ventricular mass index and diastolic function**
The mean left ventricular mass index at the start of open label nifedipine treatment was 97.8 g/m² (sem ± 1.9) and reduced to 91.7 g/m² (sem ± 1.9) after 26 weeks of treatment in the simvastatin group and 88.5 g/m² in the placebo group. The change of left ventricular mass index after 2 years of simvastatin and nifedipine treatment was –19.0 g/m² (sem ± 1.74), compared to –14.3 g/m² (sem ±1.69) in the placebo and nifedipine group. There was a borderline significant difference between both groups, in favor of the simvastatin and nifedipine group with P =0.0548. The mean E/A ratio at the start of open label nifedipine treatment was 1.04 (sem ± 0.02) and did not
significantly change after 26 weeks of treatment (change of 0.028 with 95% CI (-0.006;0.061) with \( P = 0.11 \). At randomization the mean E/A ratio was 1.05 (sem ± 0.03) in the simvastatin group, and changed to 1.09 (sem ± 0.02) after 2 years (change of 0.06 sem ± 0.03). In the placebo group, mean E/A ratio at baseline was 1.04 (sem ± 0.04) and changed to 1.16 (sem ± 0.05) after 2 years of treatment (change 0.09 sem ± 0.03). Changes of E/A ratio did not differ between both groups (\( p \)-value of 0.49).

**Effect of treatment on intima media thickness**

The change of mean max far wall IMT in the simvastatin group was not significantly different compared to placebo, as seen in table 4. Also, the combined mean far wall IMT in both groups did not change after treatment either. The mean mean far wall IMT at baseline was 0.74 mm (sem 0.02) and increased to 0.80 (sem 0.02) after two years in the simvastatin group. The mean mean far wall IMT at baseline was 0.77 (sem 0.02) and increased to 0.81 (sem 0.02) in the placebo group. The change of mean mean far wall IMT at the end of the study was 0.06 (sem 0.02) in the simvastatin group was not statistically different compared to 0.03 (sem 0.02) in the placebo group, with \( P = 0.22 \). When arterial segments were analysed separately, the effects of simvastatin versus placebo on IMT were similar.

Change in mean maximum IMT was not correlated with change in left ventricular mass (\( r = 0.02 \) with \( P = 0.87 \)), nor with changes in ambulatory systolic and diastolic

| Table 4 Combined maximum far wall intima media thickness of carotid and femoral segments (mm) |
|---------------------------------------------|-------------|-------|--------|-------|
|                                            | N   | Mean  | SE    | Median | P-value|
| Simvastatin                                |     |       |       |        |
| Randomisation                              | 50  | 0.93  | 0.02  | 0.90   |
| End                                        | 46  | 1.00  | 0.03  | 0.96   |
| Placebo                                    |     |       |       |        |
| Randomisation                              | 50  | 0.96  | 0.03  | 0.91   |
| End                                        | 45  | 1.01  | 0.03  | 0.93   | 0.2214 |

P-value, change in mean max far wall IMT simvastatin versus placebo
Effects of simvastatin besides nifedipine

blood pressures ($r = 0.05$ with $P = 0.62$ and $r = 0.009$ with $P = 0.92$, respectively).

**Reproducibility**
Ten, randomly chosen patients were reexamined, in order to reveal the measurement of variation. The measurement error of variation of the mean max far wall IMT at baseline was $0.07$ mm. After 26 weeks of treatment a second reproducibility study with the same ten patients revealed a measurement error of variation of $0.04$ mm.

**DISCUSSION**

Addition of simvastatin after 26 weeks of nifedipine treatment in patients with hypertension and persisting mild moderate hypercholesterolemia led to an unexpectedly larger decrease of left ventricular mass. No effect on intima media thickness was found. It must be kept in mind that the 26 weeks open label treatment with nifedipine alone had already reduced left ventricular mass and intima media thickness with $9\%$. Thus, the greatest remodeling of cardiovascular structure had already taken place. Subsequently, addition of simvastatin to nifedipine treatment had minimal effects on 24 hour ambulatory blood pressure and intima media thickness.

A study by Su et al. supports our finding, by showing that pravastatin had an additional effect on reducing LV mass, independent of lipid-lowering effects$^{19}$. The mechanisms of left ventricular mass reduction by simvastatin might induce LV mass reversal remain unclear. Hyperlipidemia has been reported to increase the collagen synthesis and deposition in the blood vessel wall$^{20,21}$, which could be partially responsible for a decrease in arterial compliance and an increase in resistance to blood flow resulting in an increased left ventricular afterload. Hyperlipidemia can stimulate the increased angiotensin II receptor expression$^{22,23}$, which in turn stimulates myocyte growth. Mechanical factors provide signals for hypertrophy as well as growth of myocardial cells$^{24}$. Structural and functional changes in peripheral arteries may further increase LV mass. Simvastatin has been shown to improve endothelial function, and might therefore lower the afterload of the left ventricle, resulting in a regression of left ventricular mass. In rabbits with hypertrophic cardiomyopathy, simvastatin induced regression of hypertrophy and fibrosis and improved cardiac function$^{25}$. Usually, the regression of left ventricular mass is associated with improvement of diastolic function. In our study, no improvement of E/A ratio was observed after treatment. This might be explained by the fact that E/A ratio was already in the normal range at baseline.
The significant reduction of LVMI after 26 weeks of nifedipine treatment, continued after 2 years of treatment in the simvastatin and in the placebo group. This further reduction of left ventricular mass was remarkable, because ambulatory systolic blood pressure slightly increased and diastolic function stabilized. The continued decrease of LVMI after two years of treatment could be the result of a better compliance of the large arteries, maybe caused by nifedipine. It has been known that nifedipine improves endothelial function in patients with hypertension and hypercholesterolemia26. Although such functional properties of the arteries are assumed, structural changes in terms of intima media thickness could not be observed in our study. In fact, not a regression but a similar progression of intima media thickness was observed after two years in the simvastatin (0.08 +/- 0.02) compared to the placebo group (0.04 +/- -0.02). This might well reflect the aging process, as in placebo arms of controlled studies intima media thickness has been reported to increase by 0.006 to 0.03 mm per year5, 6. In the active treatment arm of statin studies, the 1 year change in intima media thickness of the common carotid artery has been valued in the range between –0.011 to –0.043 mm27. Thus, the change in intima media thickness in our simvastatin group is quite remarkable as cholesterol levels were significantly lowered by simvastatin compared to placebo treatment. On the other hand, functional changes like the antiproliferative effects of statins on resistance vessels may have improved arterial compliance. We did not measure functional vascular measurements, but it has been known that statin treatment is associated with a restoration of endothelial function28 and improvement in myocardial perfusion29. These cardiovascular benefits could reduce cardiac afterload and improve systolic function, resulting in regression of left ventricular mass.

The effect of calcium channel blockers as a preventive therapy of the atherosclerotic process was evaluated in the INTACT study11, using nifedipine, in the Montreal study30 using nicardipine, and in the PREVENT study31-33 using amlodipine. All these studies used consecutive coronary angiography. Although the former 2 studies demonstrated a modest benefit in preventing the progression of new lesions only, the latter revealed no effect whatsoever. By tracking plaque progression with angiography, a significant amount of information is lost because only the protruding portion of the plaque is demonstrated, which could be an important reason why minor or no changes were found in those studies. In PREVENT study, in which intimal medial thickness of the carotid artery was measured directly by using ultrasound, the calcium channel blocker amlodipine was found to inhibit intimal medial progression in type 2 diabetes. Recently, the INSIGHT study showed a difference in early carotid wall changes using ultrasound in favor of nifedipine compared to co-amilorizide after 4 years of treatment in hypertensive patients13.
We did not measure diameter changes. These diameter changes may influence wall thickness and they occur early after start of antihypertensive therapy, when blood pressure is lowered. They remain relatively stable without progression as the IMT changes. The fact that similar trends over two years were observed in the IMT for simvastatin and placebo in our study makes it unlikely that carotid diameter changes have obscured differences between both agents on IMT.

Whether the decrease in IMT after 26 weeks of open label nifedipine treatment before randomization to simvastatin or placebo is due to functional vasodilatation rather than structural changes remains unclear. Ultrasound imaging cannot discriminate between the intimal layer and the medial layer of the vessel wall to distinguish true atherosclerosis viewed as a disorder restricted to the intimal layer versus the adaptive response of the medial layer to changes in tensile stress such as during hypertension. Our findings of the effects of simvastatin compared to placebo treatment on intima media thickness in these patients suggest that the medial layer had been regressed by nifedipine treatment. Furthermore, the medical effect on the intimal layer, as in atherosclerosis, seems limited. These findings support the view that in combined hypertension and mild hypercholesterolemia tensile stress is a major factor in determining the intima media thickness, as assessed by B-mode ultrasound.

In conclusion, a significant reduction of left ventricular mass and intima media thickness was observed after nifedipine alone, but the subsequent addition of simvastatin resulted in further reduction of left ventricular mass index. Thus, assessment of left ventricular mass in statin studies seems warranted in at least specific patient groups, and may even reveal larger structural changes than those of large blood vessels. Whether this effect of statins on left ventricular structure is associated with reductions in cardiovascular morbidity and mortality in such subgroups remains to be established.
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