Effects of initial and long-term lipid-lowering therapy on vascular wall characteristics

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Abstract

Several studies have demonstrated the beneficial effects of 3 hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors on vascular properties, but little is known about treatment intensification. We compared patients in whom statins were started (INITIAL, n = 30) for hypercholesterolaemia (> 6.5 mmol l⁻¹) with a matched patient group of long-time statin users, with similar baseline characteristics for lipids, intima-media thickness (IMT), and pulse wave velocity, in whom treatment with statins was intensified (LONG-TERM, n = 54). At baseline and after 1 year, lipid profile, IMT of the carotid and femoral arteries, aortic distensibility using pulse-wave velocity and various properties of the peripheral vascular bed using a recently developed bio-impedance method were measured. After 1 year the relative changes in lipid profile were significantly better in the INITIAL compared with the LONG-TERM-group. The relative changes in IMT of the mean internal carotid and common femoral arteries significantly differed between the INITIAL and LONG-TERM-group (−8 and +11%, −11 and +22%, respectively). After 1 year, in both groups, most other vascular wall characteristics were unaltered compared with baseline. In conclusion, the beneficial structural alterations of the vascular wall were greater after starting than after intensifying already existing lipid-lowering treatment. This suggests that other effects of HMG-CoA reductase inhibitors than lipid-lowering alone must be involved in vascular changes. © 2001 Elsevier Science Ireland Ltd. All rights reserved.

Keywords: Hypercholesterolaemia; Lipid-lowering drugs; 3 Hydroxy-3-methylglutaryl-coenzyme reductase inhibitor; Clinical trial; Intima-media thickness; Vascular wall

1. Introduction

Several clinical trials have demonstrated favourable effects of lipid-lowering therapy on cardiovascular morbidity and mortality, and on coronary atherosclerosis measured by quantitative coronary angiography [1,2]. Lipid-lowering therapy also showed beneficial effects on both structural and functional properties of the vascular wall, using non-invasive vascular measurements. Some placebo-controlled trials assessed the effect of lipid-lowering therapy during 2–4 years on the intima-media thickness (IMT) of the carotid and femoral arteries, measured by high resolution B-mode ultrasound [3], on the endothelial function of the brachial artery and on the arterial distensibility of the carotid artery [2,4–7]. The observed vascular changes appeared to be usually related to the degree of lipid-lowering, even when additional effects of lipid-lowering drugs independent of lipid reduction were assumed to be operative [8–10]. Thus, lipid target values have now become a major issue and have initiated several ongoing studies comparing the effects of starting with low versus high doses of statins. However, the use of these 3 hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors has become widespread in clinical practice, the dose usually being lower than that used in the high dose studies described above. Therefore, posi-
tive results of high dose studies may result in treatment intensification in many patients.

The aim of this study was to compare retrospectively changes in vascular wall characteristics after intensifying treatment, with those after starting lipid-lowering drugs. If the effect of statins on the vessel wall would be independent of the degree of lipid-lowering, intensifying treatment might be less effective than expected. We compared starting and intensifying treatment in previously untreated and in conventionally treated hyperlipidaemic patients, respectively, on various vascular characteristics.

2. Methods

2.1. Study population and design

The study population consisted of participants of the Dutch project On Cardiovascular Tracing Of Risk factors, Bristol-Myers Squibb (DOCTOR)-study, a study which evaluated the effects of reducing cardiovascular risk factors on changes of clinical and biochemical cardiovascular risk parameters. In our Out-patient Clinic for Atherosclerosis/Lipid Disorders, in the years 1995–1996, 84 patients were recruited with untreated or treated moderate to severe hypercholesterolaemia. Moderate to severe hypercholesterolaemia was defined as a fasting plasma total cholesterol between 6.5 and 12.0 mmol 1 \(^{-1}\), resistant to diet or lipid-lowering therapy. Inclusion was independent of a history of cardiovascular events or use of cardiovascular drugs. Patients with a medical history of unstable angina pectoris, poorly controlled congestive heart failure, diabetes mellitus, impaired renal or hepatic function, rheumatoid arthritis and drugs or alcohol abuse were excluded. The use of both simvastatin or pravastatin as HMG-CoA reductase inhibitor was allowed. The dose was titrated with the aim to reduce total cholesterol <5.0 mmol 1 \(^{-1}\) and/or low-density lipoprotein (LDL)–cholesterol <3.5 mmol 1 \(^{-1}\). To reach this treatment goal, combination therapy was given with other lipid-lowering drugs such as fibrates, bile acid resins or niacin if necessary. At baseline and after 1, 3, 6 and 12 months, fasting lipid profile and blood glucose was determined and the lipid-lowering medication adjusted if needed. Non-invasive vascular measurements were made at baseline and after 1 year.

2.2. Patients characteristics

Participants were divided retrospectively into two groups according to their treatment status at inclusion in the study. One group consisted of previously untreated patients in which treatment with lipid-lowering drugs was initiated for the first time (INITIAL) and another group consisted of patients using lipid-lowering therapy in which lipid-lowering treatment was intensified (LONG-TERM). Body mass index (BMI) was calculated by dividing the body weight by the square of the length (kg m \(^{-2}\)). The existence or absence of cardiovascular disease was recorded using patient histories. Coronary heart disease (CHD), cerebrovascular accidents (CVA), peripheral vascular disease (PVD) and a family history of cardiovascular diseases were defined according to current clinical practice. Smoking was classified as ‘never’, ‘formerly’ for patients who stopped smoking before participation in the study for at least 3 years, and ‘currently’ for patients who continued smoking.

2.3. Biochemical parameters

After an overnight fast, blood samples were taken to measure glucose, cholesterol, high-density lipoprotein (HDL)–cholesterol, triglyceride and lipoprotein(a) using standard laboratory methods. LDL–cholesterol was calculated by the Friedewald formula [11] and the cholesterol/HDL–cholesterol ratio by dividing total cholesterol by HDL–cholesterol.

2.4. Non-invasive vascular parameters

The parameters were obtained by two observers (vascular technicians) blinded to the assignment of the patients to the INITIAL or LONG-TERM-group.

Blood pressure was measured after 5 min of rest in sitting position, using a calibrated automatic oscillometric manometer (mmHg).

The IMT was measured using high resolution B-mode ultrasound (Acuson XP128 duplex scanner) [12]. In supine position, the far wall of different segments of the carotid arteries (common carotid artery (CCA) and internal carotid artery (ICA) and the carotid bulb (CB)) and the right common femoral artery (CFA) and superficial femoral artery (SFA) were scanned and assessed. The IMT was defined as the distance between the intima and media double line pattern, expressed in millimetres and reported as mean value of the right and left side.

Aortic distensibility (\(D_{ao}\)) was determined with pulse-wave velocity measurements as extensively described elsewhere [13], using a computerised program, developed in our department [14,15]. Two Doppler probes (5 MHz each) were placed on conducting gel upon the proximal part of the right subclavian artery and the right common femoral artery just below the inguinal ligament. Simultaneous registration of the Doppler pulses was made three times during 10 s with in the meantime withdrawal of the Doppler probes from the skin. \(D_{ao}\) (in MPa \(^{-1}\)) was calculated from the time delay between the points of intersection of the systolic
upstrokes of the maximum flow velocity waveforms recorded by each Doppler transducer and the distance between the top of the manubrium sterni and the right common femoral artery as a measure of the aortic length.

Various properties of the upper arm vascular bed were investigated using an electrical bioimpedance method as described previously [16]. In brief, two potential measuring electrodes were applied around the left upper arm, with a specially designed blood pressure cuff around them. Likewise, two current conducting electrodes were placed around the proximal and distal part of the left arm. A continuous blood pressure registration at the left upper arm was made using a Finapres device (Ohmeda 2300) at the right hand, and correcting the recorded values for left–right and hydrostatic blood pressure differences. During a measurement, the cuff was rapidly inflated to 20 mmHg above the maximal systolic blood pressure, subsequently the cuff pressure was kept constant during 2 min, after which the cuff was slowly deflated in 4 min. From the concomitant changes in electrical impedance, measured by a Minnesota impedance cardiograph (model 304A; Instrumentation for Medicine), and the transmural pressure values, calculated by subtracting the cuff pressure from the mean arterial blood pressure, various physiological parameters are estimated. Parameters used in this study were the arterial bloodvolume (V), compliance (C) and distensibility (D). Their values at ambient blood pressure level are represented by V₀, C₀ and D₀, respectively. The values at zero transmural pressure (V₀(0), C₀(0) and D₀(0)) are used as representatives of the largest arteries, and at higher transmural pressures, for example 80 mmHg (V₀(80), C₀(80) and D₀(80)), as representatives of the arterial bed as a whole. The initial venous blood volume and the extravascular volume are denoted by Vₑ and Vᵥ, respectively. The cuff pressure at which the veins start to refill during cuff deflation is denoted by Pₑ₀. The difference between the reciprocal values of the impedances before and after cuff pressure changes (Yₑ₀) is used as a measure of the myogenic response (reverse stress relaxation or delayed compliance) of the arm veins and expressed as a venous blood volume (Vₑ₀). The mean arterial pressure and mean heart rate during the measurement are described by Pₑₑ and MHR, respectively. The repeatability of this method was comparable with established methods and within the physiologically acceptable range [17].

2.5. Statistical analysis

Statistical tests were performed with SPSS version 8.0. Results are given in mean ± S.D. and interquartile ranges for the duration of existing lipid-lowering therapy. Differences in baseline clinical characteristics between both groups of patients were determined by ANOVA. Paired t-tests were used to compare the biochemical and vascular parameters before and after 1 year in each of the defined groups of patients. Absolute and relative changes after 1 year were compared with both groups using multiple-comparisons. Univariate regression analysis was performed to determine different correlations of the vascular wall characteristics at baseline and after 1 year. Relative changes in biochemical and vascular parameters were defined as the percentages of the differences with regard to the initial values divided by the initial values, multiplied by 100. Differences were considered statistically significant at P-values < 0.05.

3. Results

3.1. Initial parameters

Baseline clinical and biochemical characteristics of patients in the INITIAL and LONG-TERM-group are mentioned in Table 1. The proportion of patients treated for secondary prevention of cardiovascular diseases was comparable in the INITIAL and LONG-TERM-group with 60 and 54%, respectively. In the

Table 1
Baseline clinical and biochemical characteristics of previously untreated (INITIAL) and previously treated (LONG-TERM) patients using lipid-lowering drugs

<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>INITIAL</th>
<th>LONG-TERM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (% male)</td>
<td>30 (70)</td>
<td>54 (69)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>48.7 ± 10.4</td>
<td>48.1 ± 9.9</td>
</tr>
<tr>
<td>Body mass index (kg m⁻²)</td>
<td>26.9 ± 3.2</td>
<td>26.7 ± 3.3</td>
</tr>
<tr>
<td>History of coronary heart disease (%)</td>
<td>47</td>
<td>52</td>
</tr>
<tr>
<td>History of cerebrovascular accident (%)</td>
<td>17</td>
<td>6</td>
</tr>
<tr>
<td>History of peripheral vascular disease (%)</td>
<td>13 #</td>
<td>2</td>
</tr>
<tr>
<td>Family history cardiovascular events (%)</td>
<td>63</td>
<td>67</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>23</td>
<td>46</td>
</tr>
<tr>
<td>Formerly</td>
<td>44</td>
<td>28</td>
</tr>
<tr>
<td>Currently</td>
<td>33</td>
<td>26</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Biochemical characteristics</th>
<th>INITIAL</th>
<th>LONG-TERM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol (mmol l⁻¹)</td>
<td>7.93 ± 1.27</td>
<td>7.67 ± 1.38</td>
</tr>
<tr>
<td>Triglyceride (mmol l⁻¹)</td>
<td>3.99 ± 3.90</td>
<td>2.61 ± 1.60</td>
</tr>
<tr>
<td>HDL-cholesterol (mmol l⁻¹)</td>
<td>0.95 ± 0.26</td>
<td>1.01 ± 0.31</td>
</tr>
<tr>
<td>LDL-cholesterol (mmol l⁻¹)</td>
<td>5.28 ± 1.47</td>
<td>5.49 ± 1.36</td>
</tr>
<tr>
<td>Cholesterol/HDL ratio</td>
<td>9.16 ± 3.98</td>
<td>8.96 ± 6.10</td>
</tr>
<tr>
<td>Lipoprotein(a) (mg l⁻¹)</td>
<td>231 ± 285</td>
<td>314 ± 326</td>
</tr>
<tr>
<td>Glucose (mmol l⁻¹)</td>
<td>4.5 ± 0.6</td>
<td>4.4 ± 0.6</td>
</tr>
</tbody>
</table>

*Values are expressed as mean ± S.D.; HDL, high-density lipoprotein; LDL, low-density lipoprotein; #, P < 0.05 between INITIAL and LONG-TERM.
INITIAL-group, more patients had a history of peripheral vascular disease ($P < 0.05$). At baseline, in the LONG-TERM-group, 23 (43%) participants were treated with pravastatin with a mean dose of 37 mg, and 28 (52%) with simvastatin in a mean dose of 44 mg, respectively. Of these patients 16 (30%) were additionally using combination therapy with one of the statins and three patients (6%) used monotherapy with other lipid-lowering drugs. Mean duration of lipid-lowering treatment was 18 (1.25–30) months. Promptly after inclusion, one patient in the LONG-TERM-group dropped out of the study because of a severe myocardial infarction.

Baseline triglyceride values were higher in the INITIAL-group. There were no other differences in lipid profile at baseline. The lipid profile of the patients in the LONG-TERM group at the start of the first lipid-lowering therapy was not significantly different from that at the moment of inclusion in the present study.

Table 2 shows the non-invasively determined vascular parameters. No significant differences were found in the mean IMT of the carotid and femoral artery in the INITIAL compared with the LONG-TERM-group, although the IMT of the CCA and CFA tended to be higher in the INITIAL-group. The myogenic response of the peripheral veins, and the extravascular volume were lower in the INITIAL compared with the LONG-TERM-group ($P = 0.018$ and 0.012, respectively). At baseline, no further differences in vascular wall characteristics between both groups were found.

Among the observed baseline correlations, the cholesterol/HDL–cholesterol ratio was positively correlated with the IMT of the mean CCA ($r = 0.36$, $P < 0.01$), but also with the $C_{a(80)}$ ($r = 0.49$, $P < 0.001$), in the overall group.

3.2. Follow-up parameters

After 1 year of treatment, in the INITIAL-group ten (33%) patients were treated with pravastatin and 20 (67%) with simvastatin in mean doses of 36 and 37 mg, respectively. Eight (27%) patients using simvastatin were additionally treated with other lipid-lowering drugs. In the LONG-TERM-group, 15 (28%) participants were treated with pravastatin and 35 (65%) with simvastatin, in mean doses of 38 and 44 mg, respectively. Eight patients using pravastatin and 17 simvastatin (in total 46%) were additionally treated with other lipid-lowering drugs. Monotherapy with other lipid-lowering drugs than HMG-CoA reductase inhibitors was prescribed in three (6%) patients in the LONG-TERM-group. After 1 year, two patients dropped out in the INITIAL and five in the LONG-TERM-group, because of moving ($n = 1$) and non-compliance ($n = 1$) in the INITIAL and psycho-social problems ($n = 1$), non-compliance ($n = 3$) and misunderstanding ($n = 1$) in the LONG-TERM-group.

After initiating or intensifying (1 year) lipid-lowering therapy, the lipid profile significantly improved in both groups, except for the triglycerides in the LONG-TERM-group. In the INITIAL-group the total cholesterol fell with 2.18 mmol $l^{-1}$ to a mean value of 5.63 mmol $l^{-1}$, in the LONG-TERM-group with 1.55 to 6.12 mmol $l^{-1}$ (not significant (n.s.) between both groups). The triglycerides fell with 0.99 to 2.85 mmol $l^{-1}$ in the INITIAL-group, and with 0.23 to 2.21 mmol $l^{-1}$ in the LONG-TERM-group (n.s. between both groups). The HDL-cholesterol rose with 0.25 to 1.22 mmol $l^{-1}$ in the INITIAL-group, and with 0.12 to 1.19 mmol $l^{-1}$ in the LONG-TERM-group ($P = 0.02$ between both groups). The LDL-cholesterol fell with 2.0 to 3.17 mmol $l^{-1}$ in

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**Table 2**

Baseline vascular characteristics of previously untreated (INITIAL) and previously treated (LONG-TERM) patients using lipid-lowering drugs*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>INITIAL ($n = 30$)</th>
<th>LONG-TERM ($n = 54$)</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure (mmHg)</td>
<td>128/81 ± 16/9</td>
<td>124/78 ± 11/7</td>
<td>n.s.</td>
</tr>
<tr>
<td>Aortic distensibility (MPa$^{-1}$)</td>
<td>11.1 ± 4.6</td>
<td>11.9 ± 4.5</td>
<td>n.s.</td>
</tr>
<tr>
<td><strong>Intima-media thickness</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CCA ($\text{mm}$)</td>
<td>0.76 ± 0.22</td>
<td>0.67 ± 0.17</td>
<td>n.s.</td>
</tr>
<tr>
<td>CB ($\text{mm}$)</td>
<td>1.05 ± 0.33</td>
<td>0.98 ± 0.39</td>
<td>n.s.</td>
</tr>
<tr>
<td>ICA ($\text{mm}$)</td>
<td>0.74 ± 0.21</td>
<td>0.65 ± 0.23</td>
<td>n.s.</td>
</tr>
<tr>
<td>CFA ($\text{mm}$)</td>
<td>1.21 ± 0.74</td>
<td>0.88 ± 0.45</td>
<td>n.s.</td>
</tr>
<tr>
<td>SFA ($\text{mm}$)</td>
<td>0.65 ± 0.29</td>
<td>0.54 ± 0.18</td>
<td>n.s.</td>
</tr>
<tr>
<td><strong>Upper arm vascular bed</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Art distensibility at $P_{a(0)}$</td>
<td>1.88 ± 0.86</td>
<td>1.70 ± 0.61</td>
<td>n.s.</td>
</tr>
<tr>
<td>Art distensibility at $P_{a(80)}$</td>
<td>25.5 ± 7.3</td>
<td>27.5 ± 7.7</td>
<td>n.s.</td>
</tr>
<tr>
<td>Venous myogenic response ($\text{ml cm}^{-1}$; $V_{dab}$)</td>
<td>0.69 ± 0.98</td>
<td>1.39 ± 1.28</td>
<td>0.018</td>
</tr>
<tr>
<td>Extravascular volume ($\text{ml cm}^{-1}$; $V_i$)</td>
<td>160 ± 104</td>
<td>249 ± 168</td>
<td>0.012</td>
</tr>
</tbody>
</table>

*Values are expressed as mean ± S.D.; CCA, common carotid artery; CB, carotid bifurcation; ICA, internal carotid artery; CFA, common femoral artery; SFA, superficial femoral artery; mean, mean value of both sides; Art, arterial; $P_{mn}$, mean arterial pressure; $P_a$, arterial transmural pressure; n.s., not significant.
the INITIAL-group, and with 1.51 to 4.1 mmol l\(^{-1}\) in the LONG-TERM-group (n.s. between both groups). The cholesterol/HDL–cholesterol ratio fell with 3.9 to 4.6 in the INITIAL-group, and with 2.1 to 5.5 in the LONG-TERM-group (\(P = 0.008\) between both groups). Baseline lipid values of the dropouts in both groups were excluded. The relative changes in lipid profile were significantly more pronounced in the INITIAL com-
pared with the LONG-TERM group as represented in Fig. 1, except for the triglyceride levels.

The relative changes in IMT of the mean ICA and CFA as well, were significantly different between both groups, with a decrease in the INITIAL and an increase in the LONG-TERM-group (Fig. 2). The absolute change in the mean ICA IMT was \(-0.08\) mm in the INITIAL-group, and \(+0.047\) mm in the LONG-TERM-group (\(P = 0.011\)). For the mean CFA the change was \(-0.25\) mm in the INITIAL-group, and \(+0.12\) mm in the LONG-TERM-group (\(P = 0.005\)).

The IMT of the other arterial segments showed the same tendency, although no statistical significance was reached. The mean heart rate increased in the INITIAL-group from \(64.1 \pm 9.1\) to \(69.7 \pm 9.1\) min\(^{-1}\) (\(P = 0.011\)) but remained unaltered in the LONG-TERM-group (\(64.5 \pm 9.4\) and \(66.1 \pm 9.4\) beats min\(^{-1}\)).

The extravascular volume tended to increase in the INITIAL, and to decrease in the LONG-TERM-group, with a nearly statistical difference in relative change between both groups (\(P = 0.059\)). Other IMT segments, mean blood pressure, \(D_{ao}\) and the upper arm vascular properties (arterial distensibility and compliance) remained largely unaltered compared with baseline in both groups.

In the LONG-TERM-group a relation was found between the decrease in cholesterol/HDL–cholesterol ratio and the fall in IMT of the CCA (\(r = 0.29, P = 0.055\)). Remarkably, no significant correlations were found between the relative changes in lipid profile and IMT or other vascular measurements.

### 4. Discussion

The present study shows that initiating lipid-lowering therapy is markedly more beneficial on the lipid profile and the IMT of the carotid and femoral arteries than intensified, long-term pharmacological lipid-lowering therapy in patients with comparable biochemical and vascular characteristics at baseline. Although the lipid profile improved in the LONG-TERM-group, several IMT segments even increased.

One year follow-up was sufficient to detect changes in the CCA IMT between both study groups. In several studies of lipid-lowering treatment, there was a tendency for changes in IMT after 6 months of active treatment with a significant reduction in IMT after 1 year [3]. So, the increase in IMT over 1 year during successful treatment in the LONG-TERM-group was unexpected, but may represent retarded progression. The increase was even comparable to that observed in the placebo arms of the several lipid intervention-IMT-studies and can therefore be seen as a reflection of an age-related increase in IMT [18]. Thus, remarkably, during 1 year of relatively successful additional contin-

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**Fig. 1.** Relative changes (%) in lipid profile after 1 year. Black and white bars, INITIAL and LONG-TERM-group, respectively (see text). CHOL, total cholesterol; TG, triglyceride; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; CHOL/HDL, cholesterol/HDL-cholesterol ratio. Significance levels denote differences in relative changes between both groups, *\(P < 0.05\); **\(P < 0.01\); ***\(P < 0.005\); ****\(P < 0.001\); n.s., not significant.

**Fig. 2.** Relative changes (%) in mean IMT after 1 year. Black and white bars, INITIAL and LONG-TERM-group, respectively (see text). CCA, common carotid artery; CB, carotid bulb; ICA, internal carotid artery; CFA common femoral artery; SFA, superficial femoral artery. Significance levels denote differences in relative changes between both groups, *\(P < 0.02\); **\(P < 0.005\); n.s., not significant.
ued lowering of lipids, the observed IMT increases. Assuming a causal relationship between the changes in IMT and lipid levels, this is unexpected. Another point in favour of an initial vascular effect of starting statins independent of lipid-lowering is the lack of correlations between changes in lipid profile and vascular wall characteristics. Others have also found this [9]. This does suggest an initial effect of statins, independently of the lipid-lowering itself. Such non-lipid effects of statins may consist of, for example, the modification of endothelial function and insulin resistance, increase in plaque stability and antithrombotic properties [8–10,19]. Furthermore, the LDL particle size may be of importance, as has been shown for cardiovascular events in various regression studies [20,21].

In most regression studies a single non-invasive vascular measurement was used. As Muramatsu et al. [5], we investigated several vascular characteristics. Three complementary techniques were used to investigate these characteristics, reflecting functional changes mainly. However, the aortic distensibility and arterial distensibility and compliance of all vessels of the upper arm bed failed to show differences between both groups. In contrast to others [5], we found an increase in mean heart rate in the INITIAL-group after 1 year of treatment. Although speculative, this could be a result of an increased sympathetic activity to compensate the therapy-induced decrease in IMT in order to maintain the same vascular diameter. Because of the lack of a relationship between changes in IMT and heart rate, other factors must have been involved also.

Both groups showed moderately severe hypercholesterolaemia, with higher cholesterol levels at inclusion in 1995–1997 than in most other vascular studies of lipid-lowering treatment in secondary or even primary prevention settings. Thus, because both groups included mostly patients with previous cardiovascular disease manifestations in particular, the LONG-TERM-group was considerably undertreated at the moment of inclusion [22]. Considering the number of patients already on the highest registered dose of pravastatin or simvastatin (40 mg daily in the Netherlands) at inclusion, and the higher number of patients treated with combination therapy also, it was expected that it would be more difficult to reach the therapeutic goals in the LONG-TERM than in the INITIAL-group. Therefore, the originally aimed intensification of the treatment in the LONG-TERM-group, resulting in a quite modest difference in lipid changes between both groups, was not realised by increasing the doses of statins in the first place, but by transition to another statin in the same dosage [23], frequently by the use of combination therapy and possibly by increased treatment compliance and alterations in time of ingestion of the medication.

The significantly higher triglyceride levels at baseline, together with the significantly more pronounced increase in HDL–cholesterol and decrease in LDL–cholesterol after 1 year of treatment in the INITIAL-group, could have been the result of a more atherogenic lipoprotein profile pattern B in the INITIAL-group compared with the LONG-TERM-group [24]. In that case however, the other observed differences in treatment effects have to be the result of the additional lipid-lowering treatment and/or life-style modifications, since statins have been shown to influence the lipid levels in a similar way in patients with different LDL subclasses [24,25]. Since the LDL particle size, HDL subfractions and other non-routine parameters of the atherogenic lipid profile were not determined, these questions could not be answered in the present study. Comparisons between two subsets of the INITIAL and LONG-TERM group (consisting of 27 and 50 patients, respectively) with similar triglyceride levels, showed similar effects of lipid-lowering therapy as in the original patient groups.

The IMT in both groups was relatively low at baseline. In most other lipid intervention-IMT-studies the mean CCA IMT was >0.8 mm, in many studies even >1.0 mm [3]. Most of these studies were performed in a secondary prevention setting, but our study also concerned mostly patients with pre-existing cardiovascular disease manifestations. Maybe the lower age of our patients than in most other regression studies is responsible. The 1 year change in the mean CCA IMT in the INITIAL-group was relatively large compared with that in other studies, and even larger for other vessel segments, especially the femoral artery. For other segments than the CCA little data are available on changes during treatment. Only in the Regression Growth Evaluation Statin Study (REGRESS) femoral arteries were followed and also showed more marked changes compared with carotid vessels [26].

A confounding factor in this study might have been the use of cardiovascular drugs. Because these drugs remained unaltered during the study period and patient’s baseline characteristics were comparable for both groups, this only can have had minimal influence on the results.

In conclusion, the beneficial effects of initiating lipid-lowering therapy on the IMT of the carotid and femoral arteries were greater than that of continuing already existing lipid-lowering treatment. As discussed above, the lipid-lowering effects of HMG-CoA reductase inhibitors could not have only been responsible for that, but other factors must have been involved also.

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References


