Intima-media thickness after pravastatin stabilizes also in patients with moderate to no reduction in LDL-cholesterol levels: the carotid atherosclerosis Italian ultrasound study

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Abstract

The Carotid Atherosclerosis Italian Ultrasound study (CAIUS), a multicenter, double-blind clinical trial, performed in 305 asymptomatic, moderately hypercholesterolemic patients, clearly demonstrated beneficial effects of pravastatin on the carotid intima-media thickness (IMT) progression. The database of the CAIUS study was examined in order to investigate the presence of a relationship, if any, between the activity of pravastatin on IMT progression rate and its hypocholesterolemic effect. Quantitative B-mode ultrasound imaging was used to quantify the individual mean maximum IMT progression rate in 3 years.

In the overall group of patients (placebo and pravastatin) covariance analysis showed that while the variable 'activity of pravastatin on IMT progression' did not correlate with the extent of LDL-C lowering ($F = 0.98$), the IMT progression did not correlate with the extent of LDL-C lowering ($F = 0.00, P = 0.98$). To further investigate this issue, the pravastatin treated group was stratified into quartiles of LDL-C reduction. In contrast to what was observed in the placebo group, in which a positive mean IMT progression rate was observed, independent of the extent of LDL-C reduction, no IMT progression

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was observed in any subgroup treated with pravastatin. No significant difference was found among quartiles and no trend could be identified. In conclusion, the effect of pravastatin treatment on carotid IMT progression rate is beneficial; however the CAIUS study demonstrated that lowering LDL-C by itself, does not explain the variability of beneficial changes in IMT. © 2151 Elsevier Science Ireland Ltd. All rights reserved.

Keywords: Pravastatin; Carotid atherosclerosis; Ultrasound; IMT progression; Long-term therapy

1. Introduction

Cholesterol-lowering with, e.g. statins, has resulted in an impressive reduction of cardiovascular events in a large number of primary and secondary prevention studies [1–3]. The reduction in events has not been, however, constantly proportional to the plasma lipid changes induced by the studied drugs [4]. Some authors suggest that the relative reductions in the final endpoints, i.e. cardiovascular death or myocardial infarction, after drug treatment are similar at widely different cholesterol lowering responses [3,5]; whereas other maintain that the degree of cholesterol reduction is proportional to the positive effect on the cardiovascular endpoints [6,7]. A poor correlation between vascular changes and baseline or on-trial lipid levels has also emerged from angiographic studies evaluating the progression of lesions at the coronary artery level [8] or, more recently, at the carotid wall level, as examined by ultrasound methodologies [9]. In addition, the inhibited progression/enhanced regression observed in coronary artery studies appears to be more closely related to the starting LDL cholesterolemia, rather than to the cholesterol lowering effect induced by the drug [8,10]. Very recent animal investigations have, on the other hand, suggested that pravastatin may exert, in primates kept at equal cholesterol levels, additional, cholesterol independent benefits, i.e. improving coronary distensibility and reducing the extension of arterial macrophage-rich plaques, more prone to rupture [11].

An opportunity to evaluate a statin’s vascular effect, independent of changes in cholesterolemia, is provided by a post-hoc analysis of the data from the CAIUS study. The CAIUS study was designed to test the efficacy of the HMG-CoA reductase inhibitor pravastatin on carotid atherosclerosis progression. In line with other similar trials [12–14], it showed a favourable effect of treatment on the carotid intima-media thickness (IMT) progression [15]. In the present study the database of the CAIUS study was examined, in order to investigate the presence of a relationship, if any, between the beneficial activity of pravastatin on IMT progression rate and its hypocholesterolemic effect.

2. Methods

2.1. Study design

CAIUS was a multicenter, parallel group, randomised, placebo-controlled, double blind clinical trial on 305 asymptomatic, moderately hypercholesterolemic patients (LDL cholesterol levels between 3.88 and 6.47 mmol/l and triglycerides level < 2.82 mmol/l) of both sexes (50% males, 50% females), 45–65 years, with at least one carotid artery lesion detected by quantitative B-mode ultrasound imaging. The rationale, study design and main results have been previously reported [15,16]. The primary outcome of the study was the difference between treatment groups, in the slope of progression of carotid artery mean maximum intima-media thickness (MM-IMT), a global summary measure widely used in epidemiological studies and intervention clinical trials. The MM-IMT is computed as the mean of the single maximum IMTs detected in up to 12 standard carotid artery walls including near and far walls of the distal common carotid, the bifurcation, and the proximal internal carotid artery.

Patients were screened in seven Lipid Clinics of Academic Medical Centers (Universities of Milan, Padua, Trieste, Bologna, Perugia, Rome and Naples). At each visit, fasting lipid profiles and other laboratory values were determined using standard procedures approved by the European Atherosclerosis Society [17]. Quality control for plasma total cholesterol (TC), triglycerides (TG) and HDL-cholesterol (HDL-C) measurements were established by using calibrated sera for cholesterol and triglyceride measurements. LDL-cholesterol (LDL-C) levels were determined using Friedewald’s formula [18].

At baseline, patients meeting all the clinical and laboratory criteria were examined ultrasonographically by certified sonographers to determine the presence of at least one qualifying carotid artery lesion (1.3 < IMT < 3.5 mm) in at least one of the 12 standard walls, the absence of anatomical abnormalities (arterial coiling and kinking), and acoustic shadowing not allowing the identification of the ultrasonic interfaces required for IMT measurements. A certified reader at
an independent Ultrasound Center (NGB) reviewed these recorded exams, where final ultrasonographic eligibility was established. Individuals meeting all the clinical, laboratory and ultrasonographic criteria, and who signed an approved informed consent, were instructed and counselled to adhere to a low-fat diet, meeting the recommendations of the European Atherosclerosis Society [17]. After a 6-week run-in period and an additional evaluation of lipid profiles, patients were randomised to either pravastatin (40-mg qd) or a corresponding placebo. Patient randomisation to one of the two treatment arms was performed at an independent Statistical Analysis Center. Before starting treatment, in order to establish baseline values, patients underwent two complete quantitative B-mode ultrasound imaging examinations, and a comprehensive set of laboratory tests and clinical evaluations.

After the baseline visits, all patients were seen every 3 months at their respective referring Clinical Centers. Drug safety was assessed at every visit and included ALT, AST, γGT, and CPK. Treatment compliance, determined by pill counts, was considered adequate when the pill intake exceeded 80% of the total.

The primary goal of the present post-hoc analysis was to investigate whether the slope of progression of MM-IMT correlated with the extent of LDL-C lowering. Moreover, in order to investigate whether this relationship could be pointed out at least as a trend, statistical analysis was also performed after stratification of patients treated with the active drug into quartiles of LDL-C response, all being compared to patients in the placebo group. The slope of progression of MM-IMT measurements of common carotid (CC-IMT), bifurcation (Bif-IMT) and common carotid plus bifurcation (CC + Bif-IMT) of the same subgroups were secondary goals.

### 2.2. B-mode ultrasound imaging protocol

Quantitative ultrasound examinations were performed every 6 months using a previously described ultrasonographic protocol [15,16]. The ultrasound exam was performed using an 8 MHz annular array ultrasound imaging system (2000 II s.a., Biosound, Indianapolis, IN). The protocol requires video recording of a complete circumferential examination of both carotid arteries in order to image near and far walls of the distal 1.0 cm of the common, the bifurcation, and the proximal 1.0 cm of the internal carotid arteries. The video-recorded examinations are interpreted centrally by readers masked to patients’ information. To avoid mixed operators bias, the patients’ initial evaluation and subsequent follow-up visits were assigned to a specific sonographer/reader pair. To define intra- or inter-operator reproducibility, the same or a different operator on a 50/50 basis repeated all baseline, 18 months and final examinations. This procedure increased the precision of the IMT slope estimates, and established the intra- and inter-operator reproducibility. Data on cross sectional and longitudinal quality control have been previously reported [15] and can also be provided, on request, in a specific separate technical report.

### 2.3. Statistical analysis

The primary goal of the present study required a statistical analysis procedure to determine the efficacy of pravastatin when compared to placebo, in changing the carotid MM-IMT progression slope over a three years period. The individual extent of LDL-C lowering was calculated as differences between baseline and the mean of all on trial measurements obtained between the 6th and 36th months of the trial. Each patient’s carotid MM-IMT progression slope was estimated by weighted linear regression of up to ten serial measurements versus time. Weights were proportional to the number of visualised arterial walls used to compute the carotid MM-IMTs. The analytical model assumes a linear progression of carotid MM-IMT. The mean carotid MM-IMT progressions of the subgroups were compared by analysis of covariance (ANCOVA). Progression rates were weighted proportionally to the inverse of the estimated variance of progression slope. Baseline carotid MM-IMTs and clinical centers were used as covariates. All statistical tests were two-sided with a significance level for the outcome measurement set at $P < 0.05$.

### 3. Results

#### 3.1. Distribution of lipid responses in treated patients

Data relative to LDL-C changes in the patients who reached the final third year examination are shown in Fig. 1.

In the placebo group, 133 patients reached the end of the follow up period and among these the individual LDL-C changes, calculated as differences between baseline and the mean of all on trial measurements, ranged from $-24.9$ to $+32.4$% with a mean value of $+1.8$%.

Of the 151 patients treated with pravastatin, 142 had the final third year visit, but six were excluded because of inadequate compliance, as assessed by pill counting. Of the 136 patients included in the analysis, 116 (76.8%) could be effectively considered as ‘responders’ (LDL-C reduction greater than 10%) whereas 20 (13.2%) showed an unsatisfactory response to therapy, with an LDL-C reduction lower than 10%. The individual response in terms of LDL-C reduction, ranged from $-47.3$ to $2.1$% with a mean value of $22.5$%.

Thus, in the whole group of placebo/pravastatin treated patients a wide range of LDL-cholesterol response have been recorded (from $-47.3$% to $32.6$%).
allowing the study of a possible relationship between LDL-C changes and progression of carotid atherosclerosis.

3.2. Covariance analysis: IMT progression versus treatment and vs LDL-C response

In order to investigate whether the effect of pravastatin treatment on the reduction of IMT progression correlated with the hypocholesterolemic effect, a covariance analysis was performed by pooling data of the placebo and pravastatin groups. This analysis showed that, while the reduction of IMT progression rate correlated with treatment \((F = 6.6, P = 0.01)\), it did not correlate with the extent of LDL-C lowering \((F = 0.00, P = 0.98)\). Regression analysis performed in the pravastatin treated group only, confirmed the lack of correlation between percentage of LDL-C reduction and IMT progression rate \((r = 0.06, \text{slope} = -0.0001 \text{mm-year/ΔLDL-C}, P = 0.54)\) (Fig. 2).

3.3. IMT progression and quartiles of LDL cholesterol response

To further investigate this issue, patients under active treatment were divided into quartiles according to their individual LDL-C response. The baseline characteristics of these subgroups as well as of placebo are shown in Table 1. No differences in any demographic or clinical characteristics or conventional risk factors were found between pravastatin subgroups and placebo as well as among quartiles. The subgroups were also similar in terms of baseline ultrasonographic measurements. In Table 2 the effects of treatment on serum lipids are
reported. The values represent the differences between baseline and means of all on trial measurements obtained between the 6th and 36th months of the trial. In the placebo group only TG levels increased slightly, but significantly, during follow-up, whereas in pravastatin treated patients aside from the expected reduction of TC and LDL-C a significant reduction of plasma levels of TG and a significant increase of HDL-C levels were recorded. No trend could be identified between the
effect of pravastatin on LDL-C levels and its effects on TG and HDL-C levels (Table 2).

Fig. 3 shows the annual MM-IMT progression rates in the placebo group and in the four quartiles considered. While in the placebo group a positive rate of progression was observed, in no subgroup treated with pravastatin was any IMT progression recorded. Moreover, neither significant differences among quartiles nor a significant trend could be detected, thus confirming

<table>
<thead>
<tr>
<th>Variables</th>
<th>Placebo</th>
<th>Pravastatin group (n = 136) quartiles of LDL-C response</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1 Quartile</td>
</tr>
<tr>
<td>Number of patients</td>
<td>133</td>
<td>34</td>
</tr>
<tr>
<td>Men (%)</td>
<td>78 (51)</td>
<td>20 (59)</td>
</tr>
<tr>
<td>Smokers (%)</td>
<td>32 (21)</td>
<td>7 (21)</td>
</tr>
<tr>
<td>Family history of CVD (%)</td>
<td>67 (44)</td>
<td>12 (35)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>55.3 ± 5.8</td>
<td>55.0 ± 6.4</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>24.6 ± 2.5</td>
<td>25.0 ± 2.6</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>134.0 ± 12.0</td>
<td>131.2 ± 10.2</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>81.0 ± 7.7</td>
<td>79.5 ± 6.7</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>71.9 ± 7.4</td>
<td>71.5 ± 9.5</td>
</tr>
<tr>
<td>Total cholesterol (mmol/l)</td>
<td>6.83 ± 0.61</td>
<td>6.63 ± 0.56</td>
</tr>
<tr>
<td>LDL-C (mmol/l)</td>
<td>4.73 ± 0.51</td>
<td>4.50 ± 0.52</td>
</tr>
<tr>
<td>HDL-C (mmol/l)</td>
<td>1.39 ± 0.29</td>
<td>1.31 ± 0.31</td>
</tr>
<tr>
<td>Triglyceride (mmol/l)</td>
<td>1.55 ± 0.55</td>
<td>1.80 ± 0.44</td>
</tr>
<tr>
<td>MM-IMT (mm)</td>
<td>1.04 ± 0.15</td>
<td>1.10 ± 0.17</td>
</tr>
<tr>
<td>CC MM-IMT (mm)</td>
<td>0.85 ± 0.14</td>
<td>0.92 ± 0.18</td>
</tr>
<tr>
<td>Bif. MM-IMT (mm)</td>
<td>1.32 ± 0.23</td>
<td>1.33 ± 0.27</td>
</tr>
<tr>
<td>CC + Bif. MM-IMT (mm)</td>
<td>1.08 ± 0.15</td>
<td>1.13 ± 0.17</td>
</tr>
</tbody>
</table>

* Continuous variables are means ± SD. Group differences were calculated by ANOVA for the continuous variables, and by Fisher’s Exact test (2 tails) for discrete variables. All P = not significant. LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; CC, common carotid; bif., bifurcation; MM-IMT, mean max-intima-media thickness.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Placebo</th>
<th>Pravastatin</th>
<th>Pravastatin group stratified into quartiles of LDL-C response</th>
<th>p† for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>1st quartile</td>
<td>2nd quartile</td>
</tr>
<tr>
<td>TC (mmol/l)</td>
<td>−0.07 ± 0.05</td>
<td>−0.99 ± 0.06**</td>
<td>−0.47 ± 0.08</td>
<td>−0.97 ± 0.15</td>
</tr>
<tr>
<td>LDL-C (mmol/l)</td>
<td>0.05 ± 0.05</td>
<td>−1.02 ± 0.05**</td>
<td>−0.31 ± 0.07</td>
<td>−0.95 ± 0.03</td>
</tr>
<tr>
<td>HDL-C (mmol/l)</td>
<td>0.01 ± 0.02</td>
<td>0.08 ± 0.02**</td>
<td>0.09 ± 0.03</td>
<td>0.03 ± 0.03</td>
</tr>
<tr>
<td>TG (mmol/l)</td>
<td>0.09 ± 0.04**</td>
<td>−0.10 ± 0.04*</td>
<td>−0.16 ± 0.08</td>
<td>−0.01 ± 0.06</td>
</tr>
</tbody>
</table>

* Data expressed as mean (± SEM), represent the differences between baseline values and the mean of all on trial measurements between 6 and 36 months.

** P < 0.0001;

† Evaluated by linear regression analysis.

‡ Trend results from stratification.
that the pravastatin effect on the reduction of IMT progression does not appear to be directly associated with the changes in plasma lipids. The majority of the other ultrasonographic outcome measures (CC + Bif-IMT, Bif-IMT, CC-IMT) provided results of similar magnitude and generally in the same direction as observed for the MM-IMT (Fig. 3).

No trend was finally observed after stratification of pravastatin treated patients into quartiles of triglyceride or HDL-C changes (Fig. 4).

4. Discussion

The mechanism(s) by which statins act at the vascular level have, as yet, not been fully elucidated. Since LDL are potent atherogenic factors which induce carotid thickening [19–22], it appears likely that any effective lipid lowering treatment should show an effect on arterial disease. A number of angiographic trials have generally confirmed the possibility to affect the evolution of coronary atherosclerosis by using either

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**Fig. 3.** Carotid IMT changes in the placebo group and in the pravastatin treated group stratified into quartiles of LDL-C lowering. Differences were analysed using data weighted for gender, baseline intima-media thickness and clinical center. MM-IMT, mean maximum-intima media thickness; CC, common carotid; Bif, bifurcation; CC + Bif., MM-IMT of CC and Bif analysed together. Values are means ± SEM.

**Fig. 4.** Carotid MM-IMT changes in the pravastatin treated group stratified into quartiles of % HDL-C or % triglyceride variation. Differences were analysed using data weighted for gender, baseline IMT and clinical center. Values are means.
hylipidemic drugs [23,24] or alternative methods for blood cholesterol lowering, such as partial ileal bypass surgery [25]. In addition, this hypothesis is also supported by studies focused on the carotid artery, which demonstrate that other lipid lowering drugs, different from the HMG-CoA reductase inhibitors, can effectively reduce carotid IMT progression [26]. Thus, as a general hypothesis, it may be inferred that pravastatin should influence carotid atherosclerosis progression through its hypocholesterolemic activity.

The results of the CAIUS study show that the effect of pravastatin treatment on carotid IMT progression rate is beneficial; however, they also demonstrate that lowering LDL-C by itself does not completely explain the variability of beneficial changes in IMT. In fact, after adjustment for treatment effects, the IMT progression does not correlate with the extent of LDL-C changes. Moreover, reduction of IMT progression is detectable in all treatment groups and it is impossible to identify a linear trend between IMT-changes and LDL-C reduction, when patients treated with the active drug are stratified into quartiles of cholesterol reduction.

In contrast to what was observed in the placebo group, in which the mean IMT progression was positive, in no subgroup on active treatment, even in that with the worst response in terms of LDL-C reduction (first quartile), positive mean IMT changes could be detected.

The reported findings derive from a post-hoc analysis and, as such, must be viewed cautiously. The issue of the possible lack of compliance in treated patients is out of question, because drug compliance with short half-life statins may not be monitored (no drug in plasma is found the morning after drug intake) [27] and all data of the large statin trials come from studies that, of necessity, inadequately monitored drug intake. However, it is interesting to note that these findings confirm, and extend to early atherosclerosis, the results of two recently published post-hoc analyses of the CARE and WOSCOPS clinical trials, which suggest that the influence of pravastatin on the event rates (mortality and CV morbidity) may not be completely explained by the reduction in LDL-C [3,5]. A similar post-hoc analysis of the 4S study, in contrast, suggests that the beneficial effects of simvastatin treatment may be determined mainly by the magnitude of LDL-C changes, but no data are offered on the variability of the LDL-cholesterol response to treatment [7]. Interestingly, in the angiographic LCAS study [28], positive coronary diameter changes occurred even in patients with very low baseline cholesterolemia, apparently unaffected in similar studies with other statins [29].

In two very recent reports from B-mode ultrasound studies carried out within large preventive studies, the relationship between cholesterolemia response and carotid wall changes was only partly evaluated [9,30]. In the LIPID study, an investigation on a subgroup of 522 patients, out of the approx. 9000 participating in this secondary prevention study with pravastatin, evaluated the common carotid wall (not intima-media) thickness after 4 years of drug/placebo treatment [9]. The overall results do not differ from those of the present study and there appears to be little difference in tertiles with different baseline LDL-cholesterolemias, but no data are provided on the carotid response vs lipid changes. In a subgroup of 255 patients of the REGRESS Study, a coronary angiographic study with pravastatin, no clear correlation between carotid IMT changes after active drug, in a similar direction as in the present study, and coronary diameter changes could be detected; no evaluation was, however, provided on the impact of lipid changes [30].

Concerning the possible mechanisms for the pravastatin effects on carotid IMT, aside from the well known linkage between plasma lipids and atherosclerotic changes, a number of other mechanisms, particularly for drugs of the statin class, have been postulated [31]. Some of these, generally grouped under the heading of ‘pleiotropic effects’, have been extensively reviewed recently [32].

Among lipoprotein related mechanisms, drug treatment could have influenced the annual IMT progression rate by reducing TG levels or raising HDL-C [33,34]. In the CAIUS study, treatment effectively induced a reduction of TG and an elevation of HDL-C levels but, similar to the case of LDL-C, no significant trend was identified when stratifying patients into quartiles of TG-reduction or HDL-C elevation (Fig. 4).

Among the suggested pleiotropic effects, a direct inhibition of arterial smooth muscle cell proliferation has been well supported [35,36]. However, the low efficacy of pravastatin in inhibiting replication of vascular myocytes in vitro and in preventing in-vivo neo-intimal formation in normocholesterolemic rabbits [37] seems to rule out this hypothesis. Finally, pravastatin may exert its antiatherogenic role by directly affecting the rate of lipid deposition in macrophages of the atheromatous plaque [38], as well as by improving defective endothelium-dependent vasodilatation [39,40] and reducing platelet-dependent thrombus formation in flowing blood [41,42].
fact, in the WOSCOPS analysis patients not responding to treatment with an LDL-C reduction also had no benefit in terms of disease incidence [5]. However, reduced arterial progression is desirable per se and may provide an early marker of atherosclerosis control. A reasonable question may be whether plasma changes may always accurately reflect body and particularly arterial cholesterol changes. Statins, in fact, while generally exerting a marked plasma cholesterol reduction, modify to a minimal extent total body cholesterol content [43,44]. While plasma changes may not accurately reflect total body and particularly arterial cholesterol content, it would be of interest to know in greater detail the possible quantitative aspects of this dissociation, that would allow better clarification of the relationship between biochemical and arterial benefits.

In conclusion, the effect of pravastatin treatment on carotid IMT progression rate is beneficial; however, the CAIUS study demonstrated that lowering LDL-C by itself does not explain the variability of beneficial changes in IMT. Models evaluating pravastatin activity on atherosclerosis progression in animals not responding in terms of LDL-C reduction [11] could be useful to define such mechanisms. Furthermore, clinical trials performed by using statins in normcholesterolemic patients prone to atherosclerosis development, e.g. with diabetes or hypertension, may allow a better definition of the role of the drug in atherosclerosis-prone patients without LDL-C elevations.

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