Effect of Intensive Versus Standard Lipid-Lowering Treatment With Atorvastatin on the Progression of Calcified Coronary Atherosclerosis Over 12 Months

A Multicenter, Randomized, Double-Blind Trial

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Background—Recent clinical trials have suggested that intensive versus standard lipid-lowering therapy provides for additional benefit. Electron-beam computed tomography provides the opportunity to quantify the progression of coronary artery calcification (CAC) in serial measurements.

Methods and Results—In a multicenter, randomized, double-blind trial, 471 patients (age 61 ± 8 years) who had no history of coronary artery disease and no evidence of high-grade coronary stenoses (>50% diameter reduction) were randomized if they had ≥2 cardiovascular risk factors and moderate calcified coronary atherosclerosis as evidenced by a CAC score ≥30. Patients were assigned to receive 80 mg or 10 mg of atorvastatin per day over 12 months. Progression of CAC volume scores could be analyzed in 366 patients. After pretreatment with 10 mg of atorvastatin for 4 weeks, 12 months of study medication reduced LDL cholesterol from 106 ± 22 to 87 ± 33 mg/dL in the group randomized to receive 80 mg of atorvastatin (P < 0.001), whereas levels remained stable in the group randomized to receive 10 mg (108 ± 23 at baseline, 109 ± 28 mg/dL at the end of the study, P = NS). The mean progression of CAC volume scores, corrected for the baseline CAC volume score, was 27% (95% CI 20.8% to 33.1%) in the 80-mg atorvastatin group and 25% (95% CI 19.1% to 30.8%) in the 10-mg atorvastatin group (P = 0.65). CAC progression showed no relationship with on-treatment LDL cholesterol levels.

Conclusions—We did not observe a relationship between on-treatment LDL cholesterol levels and the progression of calcified coronary atherosclerosis. Over a period of 12 months, intensive atorvastatin therapy was unable to attenuate CAC progression compared with standard atorvastatin therapy. The possibility remains that the time window was too short to demonstrate an effect. (Circulation. 2006;113:427-437.)

Key Words: cholesterol • atherosclerosis • drugs • hypercholesterolemia

Lowering of LDL cholesterol levels has been established as an effective therapy for patients with ischemic heart disease or equivalent high-risk status. Recent clinical trials have suggested that intensive versus standard lipid-lowering therapy with the goal of achieving LDL cholesterol levels as low as 70 mg/dL provides for additional benefit in some patient populations1–7; however, more data are needed to define the mechanisms and potential benefits of intensive lipid-lowering therapy.5–7

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The progression of coronary atherosclerosis has frequently been used as a surrogate end point in clinical studies. The
underlying rationale was provided by studies that demonstrated that the angiographic progression of coronary artery disease was one of the most important predictors of future coronary events.8,9 Indeed, it has been suggested that the mechanisms that underlie the acute coronary syndromes, in particular coronary plaque rupture, also have an important role in the progression of coronary atherosclerosis.10,11 There is a close relation between the progression of coronary atherosclerosis and LDL cholesterol levels. Compared with a “standard therapeutic dose” of pravastatin 40 mg/d, an intensified regimen of atorvastatin 80 mg/d halted the progression of coronary atherosclerosis as determined by serial intravascular ultrasound (IVUS) interrogation in patients with significant (stenotic) coronary artery disease.4

Traditionally, coronary atherosclerosis could only be examined by invasive techniques such as coronary angiography and IVUS. With the advent of electron-beam computed tomography (EBCT), a noninvasive approach to imaging of the coronary arteries has become feasible.12 Recent expert statements list the EBCT-derived quantity of coronary artery calcification (CAC) as a modality to measure the extent of coronary atherosclerosis.13,14 A number of observational studies have analyzed the natural history of CAC. Depending on patient history and medication, rates of progression ranging between 24% and 52% per year have been reported.15–20

Patients with an increased rate of CAC progression appear to have a substantially higher risk of future myocardial infarction than patients with less progression.21–23 Some but not all observational studies have suggested an important influence of LDL cholesterol levels and statin therapy on the progression of CAC.16,18,24 The first published study with a prospective design reported that patients who had been observed for 1 year with no lipid-lowering therapy had CAC progression of 25%, whereas with prospectively initiated cerivastatin therapy during the second year, progression was significantly reduced to ~9%.25 Against this background, we performed a prospective, randomized trial to compare CAC progression over 12 months in patients with cardiovascular risk factors and at least moderate calcified coronary atherosclerosis who had no evidence of high-grade coronary stenoses and who received a standard dose of 10 mg or, in the intensive-treatment group, 80 mg of atorvastatin per day.

Methods

Study Design Overview

The study hypothesis was that therapy with atorvastatin 80 mg/d would slow CAC progression over 12 months compared with standard therapy with 10 mg/d. This hypothesis was tested in a prospective, double-blind, randomized, parallel-group, multicenter clinical trial. The primary end point was the percent change in EBCT-determined total CAC volume score between baseline and final determination (after 12 months of atorvastatin treatment). The participating patients were selected according to (1) their risk status (at least 2 risk factors in addition to the lipid profile requirements), (2) the absence of high-grade coronary stenoses (angiographically defined as $\geq 50\%$ diameter lumen narrowing) as demonstrated by invasive coronary angiography or a normal result of noninvasive exercise stress testing (testing modality optional) to avoid confounding by revascularization therapy, and (3) a CAC score according to the Agatston method $\geq 30$ to avoid the issue of interscan variability observed in patients with low Agatston CAC scores.26–27

To ensure that patients met target LDL cholesterol levels,13 an open-label 4-week run-in phase during which all patients received 10 mg of atorvastatin was included. The first EBCT examination was performed within 14 days before or after screening. Patients who had a CAC score $\geq 30$ and LDL cholesterol levels $< 130$ mg/dL at the end of the run-in phase were randomized to receive 80 or 10 mg of atorvastatin per day for 12 months. The second EBCT scan was performed after the 12-month randomized treatment phase. Figure 1 shows an overview of the study design.

The study initiated by the investigators. The study protocol was developed in collaboration between the steering committee and the study sponsor. All patients gave written informed consent, and the study was approved by the local research ethics committees of all participating institutions. In addition, a review was obtained from the German Federal Agency for Radiation Safety (Bundesamt für Strahlenschutz). On the basis of a positive vote from this agency, all German local authorities responsible for radiation safety approved the study.

Patients

Men and women aged between 32 and 80 years were screened for participation in the study. Because the EBCT patient table was only approved to support up to 115 kg, this was determined as the upper weight limit. Patients were only included if they had no history of myocardial infarction or coronary revascularization. The absence of hemodynamically relevant stenoses had to be demonstrated either by an invasive angiogram obtained within 2 years before screening (demonstrating the absence of stenoses with $\geq 50\%$ diameter lumen narrowing) or by an exercise stress test with no signs of ischemia within 6 months before screening. For inclusion in the study, LDL cholesterol levels had to range between 130 and 250 mg/dL. In the absence of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor therapy or between 100 and 130 mg/dL under therapy with HMG-CoA reductase inhibitors. Triglyceride levels $< 400$ mg/dL were required. In addition, patients had to have at least 2 cardiovascular risk factors, defined as (1) current or former smoking, (2) systemic hypertension (seated systolic blood pressure $\geq 140$ mm Hg or diastolic blood pressure $\geq 90$ mm Hg on at least 2 measurements or current antihypertensive medication use), (3) LDL cholesterol levels $\geq 160$ mg/dL, (4) HDL cholesterol levels $< 45$ mg/dL, (5) type II diabetes mellitus, or (6) a positive family history of ischemic heart disease (documented myocardial infarction or sudden cardiac death before age 55 years in male or before age 65 years in female first-degree relatives).
Accordingly, a volume of 0.13 mm³ was reconstructed because of the pixel size, i.e., 0.51 mm for the 26-cm² field of view.

Isotropic interpolation. The input data set was sampled at several volumes of 3 or more adjacent pixels. A CAC volume score was derived by the threshold of a CT density of 130 Hounsfield units (HU) in an area of calcification per coronary segment and a factor rated 1 was used as the EBCT inclusion criterion. This score is a product of the area of calcification per coronary segment and a factor rated 1 through 4 dictated by the maximum calcium CT density within that segment.

Blinded analysis of EBCT examinations was performed by the EBCT core laboratory. The quality of the scans was categorized as “good,” “moderate” (that is, not good but readily evaluable), or “not evaluable.” In scans with good or moderate quality, the calcium volume score was computed with the NetraMD workstation package (ScImage). This workstation has been used previously in studies on the reproducibility and progression of CAC.

A total of 1026 patients were screened at 55 sites in 3 countries (Germany, England, and Russia), and 471 patients (46%) entered the randomized treatment phase (Figure 2). Most screening failures were due to Agatston CAC scores <30 (n = 395) or failure to meet the lipid profile criteria (n = 74). A total of 235 patients were assigned to the 80-mg atorvastatin group and 236 patients to the 10-mg atorvastatin group. In the former group, 187 patients completed the study;
in the latter group, 202 patients completed the study. Inferior EBCT image quality led to the exclusion of further patients from the primary analysis, mainly because parts of the coronary arteries were not depicted on the scans, which rendered accurate CAC scoring impossible.

Among the patients who completed the study, EBCT analysis was possible in 175 patients in the 80-mg atorvastatin group and 191 patients in the 10-mg atorvastatin group. Demographics in the 2 treatment groups are given in Table 1. A difference between the groups was observed in the distribution of low HDL cholesterol levels and a family history of ischemic heart disease; otherwise, the 2 treatment groups had similar baseline characteristics. In particular, there was no difference in EBCT-derived CAC scores (Table 2).

Table 3 and Figure 3 give the course of the risk factor variables. Compared with 10 mg/d atorvastatin, 80 mg/d atorvastatin further reduced LDL cholesterol levels by \(\approx 20\%\). There was an overall reduction in high-sensitivity C-reactive protein, with a tendency for greater reductions in the 80-mg atorvastatin group. Despite a significant difference in LDL cholesterol values, the primary end point did not differ between the 2 groups. The mean progression of CAC volume scores, corrected for the baseline CAC volume score, was \(25\%\) (95% CI 19.1% to 30.8%) in the 10-mg atorvastatin

*One patient was randomized but did not receive run-in medication

**Figure 2.** Patient disposition.
group and 27% (95% CI 20.8% to 33.1%) in the 80-mg atorvastatin group (P=0.6477). Figure 4 shows log-transformed CAC volume scores in the 2 treatment groups, with no significant difference between the groups. Table 2 gives CAC volume scores and Agatston CAC scores at baseline and at the end of the randomized treatment phase. Of note, there was virtually no difference in CAC progression whether determined by volume or by Agatston scores (Pearson correlation coefficient, r=0.898). The finding of no difference between the 2 treatment groups in the primary analysis was confirmed by the sensitivity analyses described above. No changes were detected in the per-protocol population (n=319) or in patients with good-quality EBCT scans (n=228). No center effect and no treatment-center interaction could be detected. In an exploratory analysis of the influence of patient characteristics on percent change of CAC, only baseline CAC scores showed a statistical association (Figure 5).

CAC progression showed no relationship with on-treatment LDL cholesterol levels (Figure 6). Also, there was no relationship with any of the other on-treatment lipid parameters.

The overall number of adverse events during the randomized treatment phase was comparable between the 2 groups. In the 80-mg atorvastatin group, 53.4% of patients experienced at least 1 adverse event. The incidence of serious adverse events was 9.8%. In the 10-mg atorvastatin group, 54.5% of patients experienced at least 1 adverse event. The incidence of serious adverse events was 12.4%. The number of study participants who discontinued the study in the randomized treatment phase because of adverse events (laboratory abnormalities included) was 27 (11.5%) in the 80-mg atorvastatin group and 21 (9.0%) in the 10-mg atorvastatin group. There was no case of rhabdomyolysis. An individual list of adverse events is given in Table 4.

## Discussion

In this prospective, randomized, double-blind study comparing the effects of 80 versus 10 mg of atorvastatin on the progression of calcified coronary atherosclerosis, no difference between the 2 treatment groups was observed. To the best of our knowledge, this is the first study with the progression of calcified atherosclerosis as a surrogate end point that compared treatment with different doses of atorvastatin. The mean annual CAC progression was on the order of 25% in both groups. There was a significantly greater reduction of LDL cholesterol levels by ≈20% in the 80-mg atorvastatin group (or, in absolute terms, 19 mg/dL). No relationship between on-treatment LDL cholesterol levels and CAC progression was observed. Also, no relationship with other on-treatment lipid values was seen. Exploratory analyses of a variety of baseline parameters that might contribute to CAC progression revealed an association only with baseline CAC scores.

### Progression of CAC

Of interest, the pattern of CAC progression was virtually identical, irrespective of determining the CAC volume score.
or the Agatston CAC score. Because the traditional Agatston CAC score employs a density factor, peak CT density importantly contributes to this score. One could have argued that with intensive lipid-lowering therapy, a “consolidation” of calcified plaque components might have led to a stable CAC volume with, at the same time, increased density, which would account for a difference in progression between the CAC volume and the Agatston score. However, the similarity in the progression of both scores did not substantiate this theory. In this respect, an experimental animal model is of interest that was performed in rhesus monkeys.28 The animals received a cholesterol-rich chow that induced progression of overall coronary plaque burden and CAC. After a change of chow that resulted in an overall regression of coronary plaques, the area of CAC stabilized. Thus, CAC progression was stopped with the reduction of cholesterol ingestion. At the same time, the percent plaque area that comprised CAC stabilized. Therefore, CAC progression would account for a difference in progression between the 80-mg atorvastatin group over a period of almost 5 years.5 In addition, a surrogate end point study that used IVUS observed a halting of coronary plaque progression over 18 months in patients treated with 80 mg of atorvastatin compared with a progression of plaque volume in patients treated with 40 mg of pravastatin.4

**Progression of Coronary Atherosclerosis**

A reliable measure of the progression of coronary atherosclerosis represents a surrogate end point of great interest. It allows for direct analysis of the influence of specific interventions on coronary atherosclerosis. For clinical trials, the number of patients and the time required to test the hypothesis can be greatly reduced. This principle has been demonstrated by recent clinical trials that used IVUS measurements of coronary plaque volume change.4,29–32 Because IVUS can only be performed in conjunction with coronary angiography, it is reserved for patients with coronary artery disease. Serial measurements of CAC progression might offer a viable noninvasive alternative, as a number of recent clinical studies have suggested.15–25

**EBCT has been established as a robust method for accurate quantification of CAC, in particular by use of the CAC volume score.15,16** Despite the promise of this technology, we were unable to verify our hypothesis that calcified coronary plaque progression would be reduced or halted by intensive versus standard-dose atorvastatin therapy. Several explanations are possible. Compared with IVUS, EBCT-derived CAC only measures 1 of several plaque components, estimated by histopathologic studies to be ≈20% of overall plaque area.33 Possibly, because it focused on only this single component, EBCT was not sensitive enough to detect subtle changes of overall plaque volume. Alternatively, the time allowed between the baseline and the final EBCT examination may have been too short; however, in previous clinical studies, changes in CAC progression were detected within

### TABLE 3. Cardiovascular Risk Factors in the Randomized Patients Who Were Available for Data Analysis

<table>
<thead>
<tr>
<th></th>
<th>Screening</th>
<th>Baseline</th>
<th>Final (Month 12)</th>
<th>Percent Change, Final–Baseline*</th>
<th>Absolute Change, Final–Baseline*</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 mg atorvastatin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL, mg/dL</td>
<td>156±42</td>
<td>108±23</td>
<td>109±28</td>
<td>2±24</td>
<td>1±25</td>
</tr>
<tr>
<td>HDL, mg/dL</td>
<td>51±13</td>
<td>52±13</td>
<td>54±14</td>
<td>3±14</td>
<td>1±7</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>225±43</td>
<td>177±22</td>
<td>183±28</td>
<td>4±15</td>
<td>6±26</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>171±89</td>
<td>141±69</td>
<td>151±75</td>
<td>15±58</td>
<td>10±62</td>
</tr>
<tr>
<td>hsCRP, mg/L</td>
<td>4±6</td>
<td>NA</td>
<td>3±6</td>
<td>16±202</td>
<td>−1±7</td>
</tr>
<tr>
<td>Fibrinogen, mg/dL</td>
<td>336±81</td>
<td>NA</td>
<td>324±80</td>
<td>−1±22</td>
<td>−12±78</td>
</tr>
<tr>
<td>80 mg atorvastatin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL, mg/dL</td>
<td>153±41</td>
<td>106±22</td>
<td>87±33</td>
<td>−16±30</td>
<td>−19±32</td>
</tr>
<tr>
<td>HDL, mg/dL</td>
<td>49±12</td>
<td>51±12</td>
<td>53±12</td>
<td>5±15</td>
<td>2±7</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>224±42</td>
<td>175±24</td>
<td>158±36</td>
<td>−9±20</td>
<td>−16±35</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>191±127</td>
<td>157±79</td>
<td>137±71</td>
<td>−4±43</td>
<td>−18±76</td>
</tr>
<tr>
<td>hsCRP, mg/L</td>
<td>4±8</td>
<td>NA</td>
<td>2±5</td>
<td>39±655</td>
<td>−2±10</td>
</tr>
<tr>
<td>Fibrinogen, mg/dL</td>
<td>333±91</td>
<td>NA</td>
<td>325±84</td>
<td>0±22</td>
<td>−8±87</td>
</tr>
</tbody>
</table>

hsCRP indicates high-sensitivity C-reactive protein; NA, not applicable. Values are mean±SD.

*If baseline not done, then % change = Final–Screening.
this time frame,\textsuperscript{16,25} and those studies detected significant
c changes in CAC progression despite a similarly great varia-
tion of CAC scores as in the present study. It thus appeared
that at least in patient groups with adequate sample size,
EBCT should offer sufficient sensitivity. Sample size esti-
mates for the present study were calculated accordingly.
In the observational study conducted by Callister et al.\textsuperscript{16},
there was an approximately linear relationship between

Figure 3. Changes in lipid parameters between screening (first visit; month −1), baseline (at the end of the open-label run-in phase;
month 0), and final visit at the end of the randomized treatment phase (month 12). Mean values and 95% CIs are shown in blue for the
10-mg atorvastatin group and in red for the 80-mg atorvastatin group. *P*<0.05 between the 2 groups.

Figure 4. Boxplot of CAC score values at baseline and at the end of the ran-
domized treatment phase in the 2 treatment groups. For better overview, log-
transformed values are shown. The line in the middle of the box denotes the
median; the box itself denotes the bor-
ders of the 25th and 75th percentiles;
and the vertical lines that project out
from the box extend as far as the data
extend, up to a distance of 1.5 interquar-
tile (75th to 25th percentile) ranges.
on-treatment LDL cholesterol levels and progression of the CAC volume score. Patients receiving HMG-CoA reductase inhibitors had less progression than patients who received no such treatment, and patients who reached LDL cholesterol levels <120 mg/dL had, as a group, no CAC progression. In the present study, no relationship between LDL cholesterol levels and CAC progression was observed. We suggest that unrelated confounding factors that were not accounted for influenced the relationship between LDL cholesterol and CAC progression in the study by Callister et al. It is possible, for example, that patients who received HMG-CoA reductase inhibitors and reached target levels (in that instance, <120 mg/dL) in general received a better treatment than their counterparts who had no HMG-CoA reductase inhibitor medication or did not reach sufficiently low LDL cholesterol levels. A similar issue may have confounded the prospective study by Achenbach et al. Because the patients in that study served as their own controls, it is possible that overall treatment during the second year (during which cerivastatin therapy was commenced) was improved compared with the first year, which was purely observational. An additional explanation, although less likely, lies in the increase in CAC scores found between the baseline EBCT scan and the end of the first year of observation in that study. Because relative CAC progression is reduced with higher baseline CAC scores, one would expect less progression during the second than during the first year.

**Lipid Parameters**

The results of the present study can also be due to potentially insufficient lowering of LDL cholesterol levels. Whereas in the TNT trial, average on-treatment LDL cholesterol in the 80-mg atorvastatin group was 77 mg/dL, it was 87 mg/dL in the present study. However, the percent reduction of LDL cholesterol and the absolute difference between the 2 treat-

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**Figure 5.** Among baseline variables, only the baseline CAC score showed a significant relationship with the CAC volume score progression. The line in the middle of the box denotes the median; the box itself denotes the borders of the 25th and 75th percentiles; and the vertical lines that project out from the box extend as far as the data extend, up to a distance of 1.5 interquartile (75th to 25th percentile) ranges.

**Figure 6.** No relationship was observed between individual progression of the LDL cholesterol values and progression of the CAC volume score.
ment groups were comparable, because baseline LDL cholesterol levels were 98 mg/dL in the TNT trial and 108 mg/dL in the present trial. Accordingly, the goal of reaching a further 20% lowering of LDL cholesterol levels compared with the 10-mg atorvastatin group was achieved in the present trial. It is also simply possible that within 12 months of therapy, no significant difference in atherosclerosis progression occurred. No other clinical prospective data on the comparative effects on atherosclerosis progression of 80-versus 10-mg atorvastatin are available that could strengthen or discard this hypothesis. Data from clinical trials such as the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA) and the Atorvastatin Diabetes Study (CARDS) suggest that 10 mg/d atorvastatin already provides for an effective therapy, with an approximately one-third reduction of major cardiovascular events compared with placebo.34,35

Recent studies have highlighted the effects of increasing HDL cholesterol levels.28 One might argue that a more effective increase in HDL cholesterol levels would have been necessary in the present study, although no such evidence was provided by other studies that examined 80-mg atorvastatin therapy.34-35 In agreement with these other trials, 80 mg/d atorvastatin did not lead to a reduction in HDL cholesterol levels.

### Direct Effects on Calcification

HMG-CoA reductase inhibitors may differentially regulate calcification within vascular tissue. In an aortic valve tissue culture, calcification was reduced via inhibition of the cholesterol biosynthetic pathway.36 However, bone cell calcification, which is also observed in vascular tissues, appeared to be paradoxically stimulated by HMG-CoA reductase inhibitor therapy.

### Patient Selection

It is possible that our finding of no difference between the 2 treatment groups was due to patient selection. Because of the inclusion criteria explained above, the present study cohort represented a relatively narrow spectrum of stable patients with moderate coronary atherosclerosis. Perhaps patients with acute coronary syndromes would have shown a different result, but this remains speculative.

### Table 4. Adverse Events With an Incidence of at Least 0.9% (2 Subjects)

<table>
<thead>
<tr>
<th>Events</th>
<th>10 mg/d Atorvastatin (n=233), n (%)</th>
<th>80 mg/d Atorvastatin (n=234), n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adverse events leading to discontinuation of study medication</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myalgia</td>
<td>5 (2.1)</td>
<td>7 (3.0)</td>
</tr>
<tr>
<td>Nausea</td>
<td>2 (0.9)</td>
<td>4 (1.7)</td>
</tr>
<tr>
<td>Gastritis</td>
<td>3 (1.3)</td>
<td>2 (0.9)</td>
</tr>
<tr>
<td>Creatine phosphokinase increased &gt;3×ULN</td>
<td>2 (0.9)</td>
<td>2 (0.9)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>...</td>
<td>3 (1.3)</td>
</tr>
<tr>
<td>AST/ALT &gt;3×ULN</td>
<td>2 (0.9)</td>
<td>2 (0.9)</td>
</tr>
<tr>
<td>New diagnosis of coronary artery disease</td>
<td>2 (0.9)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>...</td>
<td>2 (0.9)</td>
</tr>
<tr>
<td><strong>Serious adverse events</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>New diagnosis of coronary artery disease*</td>
<td>5 (2.1)</td>
<td>2 (0.9)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>2 (0.9)</td>
<td>...</td>
</tr>
<tr>
<td><strong>Cerebrovascular disease</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prolonged reversible ischemic neurological deficit</td>
<td>2 (0.9)</td>
<td>...</td>
</tr>
<tr>
<td>Stroke</td>
<td>1 (0.4)</td>
<td>...</td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>1 (0.4)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td><strong>New diagnosis of peripheral vascular disease</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carotid artery stenosis</td>
<td>1 (0.4)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Femoral artery stenosis</td>
<td>...</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>1 (0.4)</td>
<td>2 (0.9)</td>
</tr>
<tr>
<td>Systemic hypertension aggravated</td>
<td>2 (0.9)</td>
<td>...</td>
</tr>
<tr>
<td>Carcinoma</td>
<td>2 (0.9)</td>
<td>4 (1.7)</td>
</tr>
<tr>
<td>Hernia</td>
<td>...</td>
<td>2 (0.9)</td>
</tr>
</tbody>
</table>

ULN indicates upper limit of normal; AST/ALT, aspartate transaminase/alanine transaminase; All event rates pertain to the safety population.

*The study protocol specified that the study be discontinued in an individual patient if an exclusion criterion developed during the course of the study. Accordingly, some patients with a new diagnosis of coronary stenosis were removed from the study, but this was dependent in part on the location of the coronary stenosis. In these latter patients, this is designated as a “serious adverse event.”
Recent Trials

In the Beyond Endorsed Lipid Lowering with EBCT Scanning (BELLES) trial, a similar EBCT scanning protocol as in the present study was used.37 Hyperlipidemic postmenopausal women were randomized to therapy with atorvastatin 80 mg/d or pravastatin 40 mg/d. In keeping with the present study, intensive statin therapy for 1 year caused a greater LDL reduction than moderate therapy but did not result in less progression of CAC. In a subgroup of participants in the St. Francis Heart Study who were all asymptomatic and whose CAC score (Agatston method) was in the highest quintile of the distribution, CAC progression was examined over a mean duration of 4.3 years.38 The treatment group received atorvastatin 20 mg/d, vitamin C 1 g/d, vitamin E 1000 U/d, and aspirin 81 mg/d. The placebo group received aspirin 81 mg/d. Despite the comparatively long treatment period and a trend for a lower event rate in the treatment group, no difference in the progression of CAC (Agatston method) was observed. These studies together with the present study suggest that the relationship between lipid-lowering therapy, LDL cholesterol levels, CAC progression, and total atherosclerotic plaque is indeed more complex than previously thought. At least over the course of 1 year, lipid-lowering therapy cannot be expected to significantly influence the progression of CAC.

Conclusions

As opposed to previous nonrandomized studies, we did not observe a relationship between on-treatment LDL cholesterol levels and the progression of calcified coronary atherosclerosis. Over a period of 12 months, intensive atorvastatin therapy was unable to attenuate CAC progression compared with standard atorvastatin therapy. The possibility remains that the time window was too short to demonstrate an effect.

Acknowledgment

This study was funded by Pfizer GmbH Deutschland. The authors would like to thank Dr Brigitte Kluth-Pepper and colleagues from Pfizer Germany for their invaluable help in realizing the study.

Disclosures

Drs Achenbach, Erbel, Knollmann, Lahiri, and Schmermund have received research grants or other research support from Pfizer. Drs Achenbach, Erbel, Moshage, and Schmermund have received speakers’ honoraria from Pfizer. Dr Knollmann has served as a consultant/advisor for Pfizer GmbH Deutschland.


The progression of coronary atherosclerosis has frequently been used as a surrogate end point in clinical studies. Electron-beam computed tomography (EBCT) allows for noninvasive analysis of the progression of coronary artery calcification (CAC). Patients with an increased rate of CAC progression appear to have a higher risk of myocardial infarction. Observational studies have suggested that elevated LDL cholesterol levels are associated with an increased progression of CAC and that statin therapy can attenuate this progression. We performed a prospective, randomized trial to compare CAC progression over 12 months in patients with cardiovascular risk factors and moderate EBCT-derived CAC scores who had no evidence of high-grade coronary stenoses and who received a standard dose of 10 or 80 mg of atorvastatin per day. After 4-week pretreatment with 10 mg of atorvastatin, 12 months of study medication reduced LDL cholesterol from 106±22 to 87±33 mg/dL in the 80-mg atorvastatin group (P<0.001), whereas levels remained stable in the 10-mg atorvastatin group (108±23 at baseline, 109±28 mg/dL at the end of the study, P=NS). There was no relationship between on-treatment LDL cholesterol levels and the progression of CAC and no difference in CAC progression between the study groups. Thus, over a period of 12 months, intensive atorvastatin therapy was unable to attenuate CAC progression compared with standard atorvastatin therapy. Our data suggest that at least over the course of 1 year, lipid-lowering therapy cannot be expected to significantly influence the progression of CAC.
Effect of Intensive Versus Standard Lipid-Lowering Treatment With Atorvastatin on the Progression of Calcified Coronary Atherosclerosis Over 12 Months. A Multicenter, Randomized, Double-Blind Trial
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Circulation. published online January 16, 2006;
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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