The spectrum of premature atherosclerosis: from single gene to complex genetic disorder
Trip, M.D.

Citation for published version (APA):
Trip, M. D. (2002). The spectrum of premature atherosclerosis: from single gene to complex genetic disorder
Effect of aggressive versus conventional lipid lowering on atherosclerosis progression in Familial Hypercholesterolaemia (ASAP): a prospective, randomised, double-blind trial

Tineke J Smilde¹, Sanne van Wissen², Hub Wollersheim¹, Mieke D Trip³, John JP Kastelein², Anton FH Stalenhoef¹

Department of ¹Medicine, Academic Medical Centre, Nijmegen, The Netherlands
Departments of ²Vascular Medicine, and ³Cardiology, Academic Medical Centre, Amsterdam, The Netherlands

Lancet 2001;357:577-581
Summary

Background: High LDL-cholesterol is a risk factor for atherosclerosis. We aimed to determine whether aggressive cholesterol lowering with statins was more effective than conventional statin treatment in this disease. We investigated the effect of high-dose atorvastatin on carotid atherosclerosis progression.

Methods: We did a randomised, double-blind clinical trial in 325 patients with familial hypercholesterolaemia. Patients were given either atorvastatin 80 mg (n=160) or simvastatin 40 mg (n=165) daily, on an intent-to-treat basis. The primary endpoint was the change of carotid intima media thickness (IMT), as measured by quantitative B-mode ultrasound, over 2 years.

Findings: The overall baseline IMT, combining the measurements of the common and internal carotid artery and the carotid bifurcation on both sides, was 0.93 mm (SD 0.22) and 0.92 mm (0.21) in the atorvastatin and simvastatin groups, respectively. After treatment with atorvastatin for 2 years, IMT decreased (-0.031 mm [95% CI -0.007 to -0.055]; p=0.0017), whereas in the simvastatin group it increased (0.036 [0.014-0.058]; p=0.0005). The change in thickness differed significantly between the two groups (p=0.0001). Atorvastatin showed greater reductions in cholesterol concentrations than did simvastatin. HDL-cholesterol concentrations increased in both groups. Both drugs were equally well tolerated.

Interpretation: Our results show that aggressive LDL-cholesterol reduction by atorvastatin was accompanied by regression of carotid intima media thickness in patients with familial hypercholesterolaemia, whereas conventional LDL lowering was not.

Introduction

High concentrations of LDL-cholesterol are a risk factor for atherosclerotic vascular disease. Clinical sequelae, however, are preceded by silent changes. B-mode ultrasound allows such atherosclerotic changes in the walls of the carotid and femoral arteries to be seen, and it has been widely endorsed and standardized for measurement of intima media thickness (IMT). Crosssectional studies indicate an association between carotid IMT and cardiovascular risk factors and the prevalence of cardiovascular disease. More importantly, in prospective studies carotid IMT was able to predict coronary artery disease (CAD). Consequently, assessment of carotid
IMT changes over time has become important in clinical intervention trials.\textsuperscript{8-10} Patients with heterozygous familial hypercholesterolaemia are at an increased risk of premature CAD. This disorder provides the framework for the relation between LDL and atherogenesis and it is frequently used as a model for lipid-lowering interventions. Results of several small studies show that carotid IMT is greatly increased in these patients.\textsuperscript{3,9,11} In heterozygous adults with familial hypercholesterolaemia, life-long treatment with lipid lowering drugs is indicated, because these drugs slow down progression of the disease, as judged by coronary angiography.\textsuperscript{12} Patient tolerance and acceptance of the combination of drugs needed to successfully lower LDL concentrations, however, is poor.\textsuperscript{13} The treatment of choice is statin, an HMG-CoA-reductase inhibitor.

In most hypercholesterolaemic patients, simvastatin can reduce LDL-cholesterol concentrations by 30-40\%.\textsuperscript{9,14,15} Atorvastatin is an inhibitor of HMG-CoA reductase, which can lower LDL-cholesterol in patients with primary hyperlipidaemia by as much as 61\% over the 10-80 mg dose range.\textsuperscript{16} We postulated that a large reduction in LDL-cholesterol would slow disease progression in heterozygous patients. Our aim was to determine whether aggressive LDL-cholesterol lowering with atorvastatin 80 mg, would slow atherosclerosis progression, as measured by carotid IMT.

\section*{Methods}

\subsection*{Patients}

The study design and baseline characteristics of the patients have been described elsewhere.\textsuperscript{17} Briefly, between 1997 and 1998, men and women aged 30-70 years with familial hypercholesterolaemia were screened for eligibility. Patients were either previously untreated or treated but with LDL-cholesterol concentrations remaining above 4.5 mmol/l. After an 8 week placebo run-in, in which all lipid-lowering drugs were discontinued, baseline measurements of lipoprotein variables and IMT were recorded. Of the 377 individuals screened, 330 could be randomised. Five of these withdrew before receiving trial medication, leaving 325 patients who were included in the intention-to-treat population. 160 and 165 patients were randomised to receive atorvastatin (66 men, 94 women), or simvastatin (62, 103), respectively (Figure 1). In both groups: 29\% (46 atorvastatin, 48 simvastatin) of patients were previously untreated; mean age was 48 years (SD 10); mean body
mass index was 26 (3) kg/m²; and mean systolic and diastolic blood pressure values were 131 (16) and 79 (8) mm Hg, respectively. Cardiovascular disease (31%), smoking (32%), and the use of concomitant medication (52%) was also equally distributed between groups.¹⁷
Protocol

The ethics committees of the centres approved the protocol and written informed consent was obtained from all individuals. Patients were allocated at random to either atorvastatin 40 mg, or simvastatin 20 mg daily, with matching placebo (two tablets per day). After 4 weeks, dose of atorvastatin was increased to 80 mg and simvastatin to 40 mg daily, with matching placebo (four tablets per day). Patients remained on this dosage for 2 years. In both groups, a resin was added to the treatment if serum total cholesterol concentrations, in two consecutive visits, remained greater than 8.0 mmol/l.

Randomisation was done from a computer-generated sequence, concealed in sequentially numbered, sealed, opaque envelopes, and kept by the hospital pharmacist of the two centres. Block size for randomisation, not previously known to the investigators, was ten. Age, bodyweight, height, sex, smoking habits, and medical history were recorded. Visits were planned after 4 weeks, 6 weeks, and every 12 weeks thereafter. At each visit, a brief physical examination was done, tablets were counted, and standard dietary instruction was given. In both groups, lipids, lipoproteins, and safety laboratory measurements were also done at each visit. Samples taken to measure concentrations of apolipoprotein B and lipoprotein(a) were stored at -80°C, and tested at the end of the study at a central laboratory. Apolipoprotein B was quantified in serum by immunoephelometry. Lipoprotein(a) concentrations were measured with the Apo-Tek Elisa (Organon Teknika, Rockville MD, USA).

The ultrasound scanning procedure and its reproducibility have been described elsewhere. In short, ultrasound examinations were done with a Biosound Phase-two real time scanner (BiosoundEsaote, Indianapolis, IN, USA) equipped with a 10 MHz transducer. Three 10 mm segments of intima media were scanned bilaterally: the distal portion of the common carotid artery, the carotid bifurcation, and the proximal portion of the internal carotid artery. IMT measurements were done for both anterior and posterior walls of the common carotid artery and the carotid bifurcation, and the posterior wall of the internal carotid artery. Images were analysed with a semiautomatic software program (Eurequa; TSA company, Meudon, France).

Statistical analysis

The number of patients needed to detect an effect over 2 years (change in mean IMT) of 0.05 mm with a power of 80%, (α=0.05, and within an individual over time, SD 0. 15 mm, was 141 per treatment group. To allow for a 10% drop-out rate, the total number of patients would amount to 313.
The primary endpoint was established as the change in mm in mean IMT after 24 months. Differences between treatment groups in change from baseline after 24 months were analysed with analysis of covariance (ANCOVA), in which the change in mean IMT is the dependent variable and the independent variables are treatment group, centre, and baseline mean IMT. Analyses were two sided, with a level of significance of \( \alpha = 0.05 \), and were done on an intent-to-treat basis. Last observation carried forward was used for patients who did not complete the study, or who had missing values after 1 or 2 years of treatment. Stepwise regression techniques were used to investigate the effect of age, sex, smoking habits, history of CAD and interactions with treatment of baseline mean IMT, and centre (with respect to change after 24 months in mean IMT).

Secondary endpoints included the percentage change from baseline in lipid indices: total cholesterol, calculated LDL-cholesterol, HDL-cholesterol, triglycerides, apolipoprotein B-100, and lipoprotein(a). These changes are reported as mean (SD). Treatment differences in the percentage changes from baseline of these indices were analysed with ANCOVA. Occurrence of adverse events and serious adverse events was compared with Fisher's exact test. Statistical analyses were done with SAS (version 6.12).

Results

45 of the 325 patients of the intent-to-treat population did not complete the study (14%) (Figure 1) because of: a wish to become pregnant (two in simvastatin group), raised transaminases (one in each group), menorrhagia (one in simvastatin group), emotional distress (two in simvastatin, three in atorvastatin group), muscle ache (two in each group), insufficient response to treatment (seven in the simvastatin and one in the atorvastatin group), death (three, two due to cardiac disease [one in each group], one to cancer [simvastatin]), incorrect inclusion in the study (one in atorvastatin, two in simvastatin group), transient ischaemic attack (one in atorvastatin group), polyarthritis (one in atorvastatin group), appendicitis (one in simvastatin group), unstable angina pectoris (two in the simvastatin and one in the atorvastatin group), withdrawal or lost to follow-up (five in atorvastatin, two in simvastatin group), pyrosis (one in each group), painful legs (one in the simvastatin group), and gastric perforation (one in the atorvastatin group). The low clinical event rate is noteworthy, and could be in part explained by the young age of our familial hypercholesterolaemia cohort. Muscle ache was reported 16 times in the
Table 1: Plasma lipid and lipoprotein concentrations in patients with familial hypercholesterolemia, before and after treatment with atorvastatin or simvastatin for 2 years.

<table>
<thead>
<tr>
<th></th>
<th>Atorvastatin</th>
<th>Simvastatin</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>baseline</td>
<td>2 years</td>
<td>change</td>
</tr>
<tr>
<td>Total cholesterol (mmol/l)</td>
<td>9.99(1.87)</td>
<td>5.73(1.31)</td>
<td>-4.26(-41.8%)</td>
</tr>
<tr>
<td>Triglyceride (mmol/l)</td>
<td>1.87(1.09)</td>
<td>1.23(0.76)</td>
<td>-0.64(-29.2%)</td>
</tr>
<tr>
<td>HDL-Cholesterol (mmol/l)</td>
<td>1.18(0.32)</td>
<td>1.32(0.39)</td>
<td>0.14(13.2%)</td>
</tr>
<tr>
<td>LDL-cholesterol (mmol/l)</td>
<td>8.00(1.83)</td>
<td>3.88(1.21)</td>
<td>-4.12(-50.5%)</td>
</tr>
<tr>
<td>Lipoprotein (a) (mg/l)</td>
<td>652(764)</td>
<td>596(645)</td>
<td>-116(-14.3%)</td>
</tr>
<tr>
<td>Apolipoprotein B (mg/l)</td>
<td>1954(417)</td>
<td>1083(316)</td>
<td>-71(-44.1%)</td>
</tr>
</tbody>
</table>

Values are mean (SD) * Atorvastatin group. †Simvastatin group. ‡Difference between atorvastatin and simvastatin groups.
Table 2: A mean intima media thickness (IMT) in different segments of carotid artery at baseline and after 2 and 2 years of treatment (only non-missing values presented). For each patient, IMT was assessed bilaterally for both carotid arteries. The change was calculated from baseline to follow-up. Values presented are mean (95% CI) for all patients randomized.

<table>
<thead>
<tr>
<th>Anatomical Segment</th>
<th>Baseline</th>
<th>2 Year</th>
<th>2 Year</th>
<th>p-value</th>
<th>Mean Change (mm) 95% CI</th>
<th>2 Year</th>
<th>2 Year</th>
<th>p-value</th>
<th>Number</th>
<th>Mean Overall (mm) 95% CI</th>
<th>2 Year</th>
<th>2 Year</th>
<th>p-value</th>
<th>Number</th>
<th>Mean Overall (mm) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right Carotid</td>
<td>1.01</td>
<td>0.93</td>
<td>0.08</td>
<td>0.08</td>
<td>-0.08 (0.10 to 0.00)</td>
<td>0.85</td>
<td>0.77</td>
<td>0.08</td>
<td>0.08</td>
<td>-0.08 (0.10 to 0.00)</td>
<td>0.90</td>
<td>0.82</td>
<td>0.08</td>
<td>0.08</td>
<td>-0.08 (0.10 to 0.00)</td>
</tr>
<tr>
<td>Left Carotid</td>
<td>1.00</td>
<td>0.93</td>
<td>0.07</td>
<td>0.07</td>
<td>-0.07 (0.09 to 0.00)</td>
<td>0.85</td>
<td>0.77</td>
<td>0.07</td>
<td>0.07</td>
<td>-0.07 (0.09 to 0.00)</td>
<td>0.90</td>
<td>0.82</td>
<td>0.07</td>
<td>0.07</td>
<td>-0.07 (0.09 to 0.00)</td>
</tr>
</tbody>
</table>
RESULTS OF THE ASAP STUDY

Figure 2. Change in intima media thickness (mm) (IMT) in the different segments of the carotid artery after 1 and 2 years of treatment with Simvastatin (S) or Atorvastatin (A).

Data are combined measurements of posterior and anterior wall on both right and left side in common carotid artery (cca), carotid bifurcation (bul), and internal carotid artery (ica). Overall IMT = mean of all preselected segments in carotid artery. Vertical bars = SD.

atorvastatin and 17 in the simvastatin group, and was never accompanied by a severe increase (three times the upper limit of normal) in creatine phosphokinase values. In total 34 individuals reported mild abdominal complaints, 18 in the atorvastatin and 16 in the simvastatin group. Both drugs were equally well tolerated, and the number of adverse events did not differ between groups.

At baseline, lipid and lipoprotein concentrations did not differ between treatment groups (Table 1). LDL cholesterol was reduced by half in the atorvastatin group and
by less than half in the simvastatin treated group after 2 years. 25 patients in the simvastatin group and four in the atorvastatin group received additional resin treatment. Compliance was over 80% in both groups.

In the regression analysis, treatment with simvastatin or atorvastatin only explained the variation in LDL reduction. HDL-cholesterol increased in both treatment groups by about 13%. Atorvastatin reduced triglyceride concentrations by 29% and simvastatin did so by 18% (table 1). Lipoprotein(a) was equally reduced in both groups, whereas apolipoprotein B concentrations were lower in the atorvastatin group than in the simvastatin group (table 1). The LDL/HDL cholesterol ratio was reduced from 7.32 to 3.12 (-57%) in the atorvastatin group versus 7.62 to 3.73 (-49%) in the simvastatin group. The LDL/apolipoprotein B ratio was reduced by 13.5% and 11.5% in the atorvastatin and simvastatin groups, respectively. LDL-cholesterol below 3.0 mmol/l was reached by 43 patients (27%) in the atorvastatin group, and by 12 (7%) in the simvastatin group. No sex differences in lipid profiles were seen.

The IMT's of the common carotid artery, carotid bifurcation, and internal carotid artery were equally distributed between treatment groups (Table 2). Over 2 years, overall IMT was reduced in the atorvastatin group, but was increased in the simvastatin group (Table 2). The treatment difference was highly significant and changes were attributable to different trends in IMT of the various segments (Figure 2).

Regression of the carotid IMT was seen in 106/160 (66%) versus 69/165 (42%) patients in the atorvastatin and simvastatin treatment groups, respectively. The change in IMT after 2 years was correlated with baseline IMT ($r=0.41$, $p=0.0001$); and with % LDL-cholesterol reduction ($r=0.14$, $p=0.01$); LDL was negatively correlated with change in IMT ($r=-0.20$, $p=0.0007$). Changes in HDL-cholesterol and lipoprotein(a) did not significantly contribute to changes in IMT. Age was negatively related to the change in IMT, with an estimated regression coefficient of -0.004 ($p=0.0001$), whereas baseline IMT was positively related to change with an estimated regression coefficient of 0.351 ($p=0.0001$), corrected for treatment and centre. Smoking, cardiovascular history, and sex did not contribute to the effect on change in IMT.
Discussion

Our data support the hypothesis that aggressive LDL-cholesterol lowering of at least 45% is warranted to modify IMT progression into regression. The primary efficacy endpoint – mean 2-year change in carotid IMT – showed significant regression in the atorvastatin group, whereas the IMT in the simvastatin group increased. We recorded a treatment effect by baseline IMT in patients with higher baseline IMT values responding better to atorvastatin than did patients with low baseline values. In previous work, we showed that patients with familial hypercholesterolaemia and severely raised LDL-cholesterol, showed regression of IMT when LDL-cholesterol was lowered by 45%.

In this study, we noted true regression of carotid atherosclerosis in two-thirds of the atorvastatin treated patients in whom LDL-cholesterol was reduced by half.

The latest NCEP guidelines and joint European recommendations endorse aggressive LDL-cholesterol lowering (to less than 2.6 and 3.0 mmol/l, respectively) in patients with established CAD. Since patients with familial hypercholesterolaemia have LDL-cholesterol concentrations in a much higher range than those with CAD, these goals are seldom met. It is encouraging that although goals are not reached, atherosclerosis regression can be seen if LDL-cholesterol lowering is sufficient.

We showed a similar increase in HDL-cholesterol in both the simvastatin and atorvastatin groups, but a more prominent reduction in triglycerides by atorvastatin. Since patients with familial hypercholesterolaemia generally have triglyceride values within the normal range, absolute differences were small and a direct contribution on IMT regression was not obvious. However, triglycerides were related to baseline IMT, and reduction of triglycerides could be important in the pathophysiology of atherosclerosis regression. Triglyceride-rich LDL is more likely to be hydrolysed to a dense particle size by hepatic lipase, and small dense LDL show an enhanced susceptibility to oxidative modification and are more atherogenic. Therefore, a reduction in triglycerides might contribute to less atherogenic LDL particles and slow atherosclerosis progression. The effects of a change in triglyceride concentration on LDL particle size and oxidisability is currently under investigation in ASAP.

The post coronary artery bypass graft (post-CABG) trial was the first randomised prospective study designed to answer the question of whether an aggressive approach to cholesterol lowering is more effective than a moderate one. In line with our findings, the post-CABG trial showed that the aggressive approach to lipid lowering is more beneficial than the more conventional method.
Since to deny patients with familial hypercholesterolaemia treatment is unethical, the annual IMT progression rate in untreated patients will remain unknown. However, on the basis of the results of the LDL-Apheresis Atherosclerosis Regression Study (LAARS), in which patients were given simvastatin 40 mg, 2 year IMT progression rate can be estimated at 0.05 mm or more. In the Kuopio Atherosclerosis Prevention Study (KAPS), the progression rate in the placebo group was 0.03 mm per year in men with an LDL-cholesterol of about 5.0 mmol/l. Thus, the recorded progression of IMT in the simvastatin group indicates a retardation of the expected progression rate. It is noteworthy that more aggressive lipid lowering with atorvastatin did not only result in retardation of progression but also actually reversed the process of IMT.

In the Asymptomatic Carotid Artery Progression Study (ACAPS) and the Monitored Atherosclerosis Regression Study (MARS), a decrease in IMT was seen with lovastatin. Both studies included patients with only moderately raised cholesterol. The 25% LDL reduction seen in ACAPS resulted in a very small but significant decrease in IMT (-0.009 mm yearly), and IMT regression in MARS (-0.026 to -0.049 mm, dependent on baseline IMT) became obvious when LDL-cholesterol was reduced by 45%. A yearly IMT progression rate of 0.03 mm or more is clinically significant, since it increases the risk of future events. Therefore, the difference of 0.066 mm in 2 years between the atorvastatin and simvastatin group is anticipated to be relevant in the reduction of future cardiovascular events. The differences in mean IMT seen in our study, were attributable to the contrasting effects of the statins in the carotid bifurcation and internal carotid artery, both preferential sites for atherosclerosis.

Although the use of a surrogate endpoint for cardiovascular disease has limitations, IMT is increasingly acknowledged as a reliable measure to predict future events, and the clinical relevance of progression of IMT as a marker for cardiovascular disease is beyond doubt. Trials to confirm the effect of aggressive cholesterol lowering on cardiovascular endpoints and death are underway but will not be available for at least another 3-5 years.

Our findings on IMT regression in patients with familial hypercholesterolaemia have implications for clinical practice. Aggressive cholesterol lowering with high-dose atorvastatin results in regression of carotid IMT. We conclude that aggressive lipid lowering is indicated, beneficial, and safe in patients with familial hypercholesterolaemia.
RESULTS OF THE ASAP STUDY

References


