The spectrum of premature atherosclerosis: from single gene to complex genetic disorder
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Citation for published version (APA):
Trip, M. D. (2002). The spectrum of premature atherosclerosis: from single gene to complex genetic disorder
Effect of atorvastatin (80mg) and simvastatin (40mg) on plasma fibrinogen levels and on carotid intima media thickness in patients with Familial Hypercholesterolemia

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Am J Cardiol 2003; in press
Introduction

Most studies with pravastatin report a decrease of fibrinogen levels, whereas no effect is seen with simvastatin or fluvastatin therapy and, in contrast, a rise is observed with atorvastatin therapy. However, a recent elegant albeit short-term comparative study with fluvastatin (80 mg), lovastatin (80 mg), pravastatin (40 mg) and simvastatin (40 mg) did not observe any differences in fibrinogen levels after 12 weeks of therapy. In contrast, atorvastatin treatment has been reported to lead to elevations of fibrinogen levels that ranged from 4% at low dose (10 mg) to as much as 46% at high dose (80 mg).

We recently reported that low density lipoprotein (LDL) cholesterol reduction by atorvastatin 80 mg over a 2 year period resulted in a striking regression of carotid intima media thickness (IMT) in patients suffering from heterozygous familial hypercholesterolemia (FH). IMT is a marker for the extent of atherosclerotic vascular disease and a predictor for coronary artery disease. The ASAP (effects of Atorvastatin versus Simvastatin on Atherosclerosis Progression) study was also prospectively defined to assess the effects of both intervention modalities (atorvastatin 80 mg and simvastatin 40 mg) on fibrinogen levels. This provided us with the unique opportunity to study these long term effects and to assess whether these changes in plasma fibrinogen levels were indeed related to IMT outcome in this trial.

Patients and methods

The design and main results of the ASAP study have been reported previously. In short, ASAP was a 2 year, 2 centre, randomised, double-blind clinical trial in 325 patients with FH. Patients were randomized to either 80 mg atorvastatin or simvastatin 40 mg daily. After an 8 week placebo run in, baseline measurements of lipoprotein parameters, fibrinogen and IMT were performed. These measurements were repeated after 2 years. Of the 325 patients in the original ASAP study population, 45 patients did not complete the study and 8 patients had missing fibrinogen data on either baseline or at 2 years. FH patients who did not complete the study did not differ significantly from FH patients who received treatment for 2 years in terms of demographic and laboratory parameters. Therefore, in this assessment 272 patients were included. The Institutional Review Boards of both centres approved the protocol and written informed consent was obtained from all participants.
Fasting blood samples were drawn at baseline and after 2 years of treatment. Lipid measurements were done at each visit. Samples taken to measure fibrinogen were stored at \(-80\, ^\circ\text{C}\), and tested at the end of the study in a central laboratory. Lipoprotein parameters included total cholesterol, (calculated) LDL cholesterol, high density lipoprotein (HDL) cholesterol and triglycerides were measured as described before.\(^{12}\) Functional fibrinogen was measured in plasma using a clotting rate method according to Clauss\(^{13}\) with reference values of 1.85 – 4.41 g/l. Measurements were performed in duplicate (coefficient of variation < 6%). The final result represents the mean of the 2 measurements.

The IMT measurement procedures have been reported previously.\(^{12}\) For the ultrasound examinations a Biosound Phase-2 real time scanner (Biosound Esaote, USA) equipped with a 10 MHz transducer was used. Three 10 mm segments were scanned bilaterally: the distal portion of the common carotid artery, the carotid bifurcation and the proximal portion of the internal carotid artery. The mean IMT represents the average over anterior and posterior walls in the common carotid artery, the carotid bifurcation and the posterior wall of the internal carotid artery, bilaterally. IMT measurements were performed of both anterior and posterior walls of the common carotid artery and carotid bifurcation and posterior wall of the internal carotid artery, bilaterally. The ultrasound scannings were made by well-trained ultrasonographers in the 2 centres. The images were stored on disk and read by independent readers blinded to any information on the patients. Images were analyzed with a semi-automatic software program (Eurequa; TSA company, Meudon, France). The intra-observer and inter-observer coefficients of variation were < 5%. During the study reproducibility was checked at regular time points.

The relative change after 2 years as compared to baseline was calculated for laboratory and IMT parameters. Mean changes within the treatment groups were tested using the paired sample t-test, the Wilcoxon test was applied for variables with a skewed distribution. Mean changes between groups were compared using the independent sample t-test and the Mann-Whitney U test was applied for variables with a skewed distribution. Icoxon signed rank test was use.

The strength of the relationship between the absolute change after two years in fibrinogen and absolute change in IMT was quantified by the Pearson correlation coefficient. Statistical analyses were performed using SAS (version 8.02, SAS Institute Inc. Cary, NY, USA).
Results

Of the 325 patients from the original intention to treat population, 45 patients did not complete the study and 8 patients had missing fibrinogen data at either baseline or at 2 years. FH patients who did not complete the study did not differ significantly in terms of demographic and laboratory parameters from FH patients who received treatment for 2 years. The baseline characteristics of the two intervention groups are summarised in Table 1. At baseline, no significant differences between treatment groups were found in either lipid or lipoprotein levels, nor in fibrinogen or mean IMT. Table 2 shows laboratory and IMT parameters at baseline and after 2 year of treatment with atorvastatin 80 mg or simvastatin 40 mg. Fibrinogen levels increased during atorvastatin and simvastatin treatment significantly with 3.6% (p = 0.0104) and 3.8% (p = 0.0077), respectively. The small difference between the two treatment groups was not significant (p = 0.91). As previously described total cholesterol, LDL cholesterol and triglycerides levels were lowered significantly within each treatment group (p<0.0001 for all parameters), whereas atorvastatin 80 mg reduced total cholesterol, LDL cholesterol and triglycerides levels significantly more than simvastatin 40 mg. The
Table 2. Fibrinogen levels (g/l) at baseline and after two years treatment with 80 mg atorvastatin or 40 mg simvastatin

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>2 years</th>
<th>% change</th>
<th>p-value*</th>
<th>p-value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td>3.44 ± 0.64</td>
<td>3.53 ± 0.69</td>
<td>3.6 ± 16.1</td>
<td>0.0104</td>
<td>0.9109</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>3.51 ± 0.66</td>
<td>3.62 ± 0.76</td>
<td>3.8 ± 16.4</td>
<td>0.0077</td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± standard deviation. * within the atorvastatin or simvastatin group; † between the atorvastatin and simvastatin groups.

mean IMT in the atorvastatin group decreased by 0.040 (SD 0.155) mm (3.0%) and increased by 0.044 (SD 0.150) mm (6.4%) in the simvastatin group. This difference between the two treatment groups was significant (p<0.0001).

In contrast, no association became obvious between the change in fibrinogen and the change in IMT over 2 years. (Figure 1) The Pearson correlation coefficient between delta fibrinogen and delta IMT was −0.03 (p=0.70) in the atorvastatin and 0.03 (p=0.76) in the simvastatin group.

Figure 1. Absolute change of fibrinogen levels in relation to absolute change of mean carotid IMT in the atorvastatin and simvastatin groups

IMT = intima media thickness
Discussion

This is the first long-term and controlled study that was prospectively defined to evaluate the effect of statin treatment on plasma fibrinogen levels and to assess whether these changes were associated with a surrogate marker for cardiovascular disease. We showed a small but significant rise of fibrinogen levels both with 80 mg atorvastatin and 40 mg simvastatin of 0.09 g/l (3.6%) and 0.1 g/l (3.8%), respectively. This small increase of fibrinogen levels is statistically significant, but definitely not correlated with the IMT changes as seen after 2 years and therefore probably clinically not relevant. Since IMT is established as a surrogate marker for future cardiovascular events, the small increase of fibrinogen levels will quite likely have no influence on future cardiovascular disease in these FH patients. Moreover, elevated LDL cholesterol levels are more relevant for cardiovascular risk in FH than fibrinogen levels. In addition, elevated fibrinogen levels are associated with high triglycerides, small dense LDL cholesterol and postprandial dyslipidemia (14), a situation not characteristic for FH.

In our study both treatment with simvastatin and with atorvastatin showed a similar increase of fibrinogen levels. This increase was statistically significant but relatively small. Some previous studies, however, showed no changes in fibrinogen levels by simvastatin but a > 40% increase by high dose atorvastatin. These discrepancies might be, at least in part, explained by the dose or the duration of the treatment, by the baseline fibrinogen values, by the heterogeneous nature of the patients recruited, or by the methods used to measure fibrinogen in the different studies.

Conclusion

Fibrinogen is an independent marker for cardiovascular disease. Increase of plasma fibrinogen induced by long term statin therapy, however, is not associated with negative effects on intima media thickness, a generally accepted surrogate marker for atherosclerosis progression.

Acknowledgements

JJP Kastelein is an established investigator of the Netherlands Heart Foundation (2000D039). The fibrinogen measurements were performed by Dr. C Kluft, Gaubius Laboratory, Leiden, The Netherlands.
Literature
