Effect of *Atorvastatin* (80 mg) and *Simvastatin* (40 mg) on Plasma Fibrinogen Levels and on Carotid Intima Media Thickness in Patients With Familial Hypercholesterolemia

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Most studies with pravastatin report a decrease in fibrinogen levels, whereas no effect has been found with simvastatin or fluvastatin therapy; however, an increase has been observed with atorvastatin therapy.[1–3] A recent elegant, but 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.[4] 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).[5–9]

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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 with heterozygous familial hypercholesterolemia (FH).[10] IMT is a marker of the extent of atherosclerotic vascular disease and a predictor of coronary artery disease.[11] The effects of Atorvastatin versus Simvastatin on Atherosclerosis Progression (ASAP) 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 related to IMT outcome in this trial.

The design and main results of the ASAP study have been previously published.[10,12] In short, ASAP was a 2-year, 2-center, randomized, double-blind clinical trial in 325 patients with FH. Patients were randomized to either 80 mg/day atorvastatin or simvastatin 40 mg/day. After an 8-week placebo run-in period, 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 at either baseline or at 2 years. Patients with FH who did not complete the study did not differ significantly from patients with FH 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 centers 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 assessed at each visit. Samples taken to measure fibrinogen were stored at −80°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 measured as previously described.[12] Functional fibrinogen was measured in plasma using a clotting rate method according to Clauss[13] with reference values of 1.85 to 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, Indianapolis, Indiana) 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 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 centers. The images were stored on disk and read by independent readers blinded to any information on the patients. Images were analyzed with a semiautomatic software program (Eurequa; TSA Company, Meudon, France). The intra- and interobserver coefficients of variation were <5%. During the study reproducibility was checked at regular time points.

The relative change after 2 years compared with baseline was calculated for laboratory and IMT pa-

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TABLE 1 Baseline Characteristics of the Patients

	Atorvastatin 80 mg (n = 136)	Simvastatin 40 mg (n = 136)	p Value
Age (yrs)	47 ± 10	49 ± 11	0.20
Men	56 (41.2%)	51 (37.5%)	0.53
Smoking	46 (33.8%)	35 (25.7%)	0.14
Cardiovascular disease	36 (26.5%)	35 (25.7%)	0.89
Body mass index (kg/m^2)	25.9 ± 3	25.8 ± 4	0.78
Blood pressure (mm Hg)	130 ± 16/79 ± 8	130 ± 15/80 ± 8	0.81/0.33
Total cholesterol (mmol/L)	10.03 ± 1.87	10.14 ± 1.87	0.62
HDL-cholesterol (mmol/L)	1.18 ± 0.33	1.17 ± 0.29	0.74
LDL-cholesterol (mmol/L)	8.04 ± 1.83	8.20 ± 1.88	0.50
Triglycerides (mmol/L)	1.56 (1.13–2.27)	1.65 (1.12–2.21)	0.95
Fibrinogen (g/L)	3.44 ± 0.64	3.51 ± 0.66	0.36
Mean IMT (mm)	0.93 ± 0.21	0.91 ± 0.20	0.43

Values are means ± SD or number (%). Triglycerides are given as median (interquartile range) because of a skewed distribution.

TABLE 2 Fibrinogen Levels (grams per liter) at Baseline and After Two Years Treatment With 80 mg Atorvastatin or 40 mg Simvastatin

	Baseline	2 yrs	% Change	p Value*	p Value†
Atorvastatin	3.44 ± 0.64	3.53 ± 0.69	3.6 ± 16.1	0.0104	0.9109
Simvastatin	3.51 ± 0.66	3.62 ± 0.76	3.8 ± 16.4	0.0077	

Values are means ± SD
*Within the atorvastatin or simvastatin group; †between the atorvastatin and simvastatin groups.

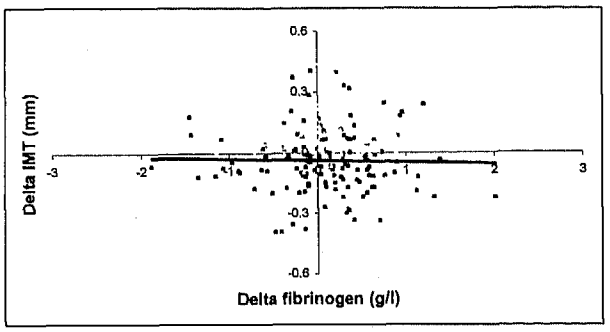

FIGURE 1. Absolute change of fibrinogen levels in relation to absolute change of mean carotid IMT in the atorvastatin *(black squares)* and simvastatin groups *(gray triangles).*

rameters. 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. Wilcoxon's sign-rank test was used. The strength of the relation between the absolute change after 2 years in fibrinogen and absolute change in IMT was quantified by the Pearson's correlation coefficient. Statistical analyses were performed using SAS (Version 8.02, SAS Institute Inc., Cary, North Carolina).

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 either at baseline or at 2 years. Patients with FH who did not complete the study did not differ significantly in terms of demographic and laboratory parameters from patients with FH who received treatment for 2 years. The baseline characteristics of the 2 intervention groups are listed in Table 1. At baseline, no significant differences between treatment groups were found in either lipid or lipoprotein levels, or in fibrinogen or mean IMT. Table 2 lists the laboratory and IMT parameters at baseline and after 2 years of treatment with atorvastatin 80 mg or simvastatin 40 mg. Fibrinogen levels increased during atorvastatin and simvastatin treatment significantly (3.6%, p = 0.0104 and 3.8%, p = 0.0077, respectively). The small difference between the 2 treatment groups was not significant (p = 0.91). As previously described, total cholesterol, LDL cholesterol, and triglycerides levels decreased 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 mean IMT in the atorvastatin group decreased by 0.040 mm (SD 0.155) (3.0%) and increased by 0.044 mm (SD 0.150) (6.4%) in the simvastatin group. This difference between the 2 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). Pearson's correlation coefficient between the Δfibrinogen and the ΔIMT was −0.03 (p = 0.70) in the atorvastatin and 0.03 (p = 0.76) in the simvastatin group.

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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 increase in 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, is not clinically relevant. Because IMT has been established as a surrogate marker for future cardiovascular events, the small increase in fibrinogen levels will quite likely have no influence on future cardiovascular disease in these patients with FH.

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] conditions that are not characteristic of FH.

In our study, treatment with both simvastatin and atorvastatin showed similar increases in fibrinogen levels. Theses increases were statistically significant but relatively small. Some previous studies, however, showed no changes in fibrinogen levels using simvastatin but did show a >40% increase using high-dose atorvastatin. These discrepancies might be partially explained by the dose or the duration of the treatment, by the baseline fibrinogen values, by the heterogenous nature of the patients recruited, or by the methods used to measure fibrinogen in the different studies.

Fibrinogen is an independent marker of cardiovascular disease. An increase in plasma fibrinogen induced by long-term statin therapy, however, is not associated with negative effects on IMT, which is a generally accepted surrogate marker for atherosclerosis progression.

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