Effect of Simvastatin Therapy on Paraoxonase Activity and Related Lipoproteins in Familial Hypercholesterolemic Patients

Marta Tomás, Mariano Sentí, Ferrán García-Faria, Juan Vila, Alex Torrents, Maribel Covas, Jaume Marrugat

Abstract—Human paraoxonase (PON1) is a calcium-dependent esterase closely associated with high density lipoprotein (HDL)-containing apolipoprotein A1 (apoAI), which has been shown to confer antioxidant properties to HDL. PON1 has been recently implicated in the pathogenesis of atherosclerosis. Low PON1 activities have been found in familial hypercholesterolemia (FH) and diabetes mellitus. We have undertaken a study of the effect of the lipid-lowering drug simvastatin on serum PON1 activity (in relation to paraoxon and arylesterase activity), on apoAI-containing and apolipoprotein B (apoB)-containing lipoproteins, and on lipid peroxide concentrations in 64 (39 women and 25 men) unrelated FH patients. We have also analyzed the influence of the PON1-192 and PON1-55 genetic polymorphisms on the response of PON1 activity to simvastatin therapy. A venous blood sample for a baseline analysis and another after 4 months of simvastatin therapy at a dosage of 20 mg per day were taken. The major effect of simvastatin on lipid traits was to decrease serum cholesterol, low density lipoprotein (LDL) cholesterol, and lipid peroxide concentrations by 19.9%, 26.3%, and 37.3%, respectively. There was also a significant decrease in serum apoB, LDL apoB, and triglyceride concentrations (20.5%, 21.1%, and 15.6%, respectively). Conversely, simvastatin had no significant influence on very low density lipoprotein–lipid content, HDL cholesterol, apoAI concentrations, and lipoprotein AI and AI:AII particles. Remarkably, serum PON1 activity toward paraoxon significantly increased during treatment with simvastatin (168.7±100.3 U/L before therapy versus 189.5±116.5 U/L after therapy, P<0.005). Arylesterase activity also displayed only a nonsignificant trend to increase after therapy. Whereas PON1 activity levels were significantly lower in FH patients before simvastatin therapy compared with those of 124 normolipidemic subjects (168.7±100.3 versus 207.6±125.2 U/L, respectively; P<0.05), this difference disappeared after simvastatin therapy. After simvastatin therapy, a significantly negative correlation between PON1 activity and lipid peroxide concentration was observed (r=−0.35, P=0.028). The latter also strongly correlated with LDL cholesterol concentration (r=0.64, P<0.001). Serum PON1 activity levels were significantly lower in the low-activity PON1-192 QQ and PON1-55 M carriers than in R carriers and in LL carriers, respectively. No significant differences were found in the therapeutic response of PON1 activity between genotype groups (8.5% and 11.1% increase for QQ homozygous and R-carrier FH patients, respectively, and 12.7% and 9.5% increase for LL homozygotes and M carriers, respectively). We conclude that simvastatin may have important antioxidant properties through increasing serum PON1 activity, perhaps as a consequence of reducing oxidative stress, by a mechanism independent of apoAI-containing lipoprotein concentration and without the influence of PON1-192 and PON1-55 genetic polymorphisms. Further studies are clearly warranted to clarify the precise mechanism by which simvastatin therapy is associated with increased PON1 activity. (Arterioscler Thromb Vasc Biol. 2000;20:2113-2119.)

Key Words: familial hypercholesterolemia ■ paraoxonase ■ PON1 genotypes ■ simvastatin

Paraoxanase (PON1) is a calcium-dependent esterase closely associated with HDL-containing apoAI that has been reported to confer antioxidant properties on HDL by decreasing the accumulation of lipid peroxidation products.1 PON1 is able to hydrolyze a number of substrates, such as paraoxon and phenyl acetate, and also lipid peroxides, cholesterol esters hydroperoxides, and H2O2; however, the physiological substrate of PON1 remains to be discovered.

It has been suggested that PON1 is related to coronary heart disease risk3,5 and that its activity, usually measured with paraoxon as a substrate, is under genetic and environmental regulation and appears to vary widely among individ-
diabetes mellitus and familial hypercholesterolemia. In diseases with accelerated atherogenesis, such as gout, individuals homozygous for the MM allele appear to have lower PON1 activity toward paraoxon.

Another polymorphism in the human PON1 gene at amino acid 55, the PON1-55 polymorphism, which contains a glutamine at position 192, whereas the high-activity PON1 R isoform contains an arginine at position 192.8

Another polymorphism in the human PON1 gene at amino acid 55, the PON1-55 polymorphism, which contains a glutamine (Q) at position 192, whereas the high-activity PON1 R isoform contains an arginine at position 192.8

Values are mean ± SD (interquartile range). NS indicates not significant.

### Methods

**Patients**

The study group consisted of 64 unrelated patients, 39 women (aged 60.1 ± 9.0 years, mean ± SD) and 25 men (aged 51.3 ± 13.2 years), with a clinical diagnosis of possible FH. The clinical diagnosis of FH was based on increased LDL cholesterol concentrations (>160 mg/dL), the presence of xanthomas in the proband or in a first-degree relative, and a positive family history of premature coronary heart disease before simvastatin therapy. PON1 activity and PON1 genotypes were also compared with those of a random population sample.

**TABLE 1.** Serum Lipid, Lipoprotein, Apolipoprotein, and Lipid Peroxide Concentrations Before and After Simvastatin Therapy in 64 FH Patients

<table>
<thead>
<tr>
<th></th>
<th>Before Treatment</th>
<th>After Treatment</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum cholesterol, mg/dL</td>
<td>305.5 ± 43.3</td>
<td>244.6 ± 40.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum triglycerides, mg/dL</td>
<td>152.2 (109.0–174.0)</td>
<td>128.5 (92.0–165.5)</td>
<td>0.005</td>
</tr>
<tr>
<td>VLDL cholesterol, mg/dL</td>
<td>18.2 ± 14.9</td>
<td>15.7 ± 20.9</td>
<td>NS</td>
</tr>
<tr>
<td>VLDL triglycerides, mg/dL</td>
<td>72.1 (41.0–90.0)</td>
<td>66.1 (32.0–89.5)</td>
<td>NS</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dL</td>
<td>236.8 ± 42.0</td>
<td>174.6 ± 38.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>49.5 ± 12.2</td>
<td>52.4 ± 11.7</td>
<td>NS</td>
</tr>
<tr>
<td>ApoAI, mg/dL</td>
<td>157.9 ± 24.1</td>
<td>161.9 ± 21.1</td>
<td>NS</td>
</tr>
<tr>
<td>ApoB, mg/dL</td>
<td>147.6 ± 25.3</td>
<td>117.4 ± 22.5</td>
<td>NS</td>
</tr>
<tr>
<td>LDL apoB, mg/dL</td>
<td>140.2 ± 22.7</td>
<td>110.6 ± 20.1</td>
<td>NS</td>
</tr>
<tr>
<td>LpAI, mg/dL</td>
<td>65.9 (59.0–76.5)</td>
<td>69.0 (59.0–80.5)</td>
<td>NS</td>
</tr>
<tr>
<td>LpAI-II, mg/dL</td>
<td>92.4 (78.0–104.5)</td>
<td>91.7 (76.2–107.6)</td>
<td>NS</td>
</tr>
<tr>
<td>Lipid peroxides, μmol/L</td>
<td>15.1 ± 11.1</td>
<td>9.5 ± 6.1</td>
<td>NS</td>
</tr>
<tr>
<td>Lipid peroxide-to-LDL cholesterol ratio</td>
<td>0.062 ± 0.043</td>
<td>0.052 ± 0.027</td>
<td>0.042</td>
</tr>
</tbody>
</table>

**TABLE 2.** Serum PON1 Activities (Toward Paraoxon and Arylesterase Activity) Before and After Simvastatin Therapy and Comparisons Between FH Patients and Controls

<table>
<thead>
<tr>
<th></th>
<th>Before Therapy</th>
<th>After Therapy</th>
<th>P</th>
<th>Controls (n = 124)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PON1 activity, U/L</td>
<td>168.7 ± 100.3</td>
<td>189.5 ± 116.5</td>
<td>0.005</td>
<td>207.6 ± 125.2*</td>
</tr>
<tr>
<td>Arylesterase activity, U/mL</td>
<td>91.1 ± 24.3</td>
<td>99.1 ± 19.5</td>
<td>0.166</td>
<td>128.5 ± 28.2†</td>
</tr>
</tbody>
</table>

Values are mean ± SD.

*P = 0.043 vs FH patients before therapy.
†P = 0.494 (not significant) for FH patients after therapy vs controls.
‡P < 0.001 for FH patients before or after therapy vs controls.
human control sera as mentioned above was used as an internal control. A unit of arylesterase activity per milliliter is equivalent to 1 μmol of phenyl acetate hydrolyzed per minute. Intra-assay and interassay coefficients of variation were 3.80% and 3.59%, respectively.

**Lipid Peroxidation**

Lipid peroxidation was measured by the thiobarbituric acid reactive substances test, as previously described. The intra-assay and interassay coefficients of variation were 4.22% and 6.8%, respectively.

**PON1-192 and PON1-55 Genotype Determinations**

Fifty FH patients from whom white cells were available underwent PON1-192 and PON1-55 genotyping in the present study. Genomic DNA was isolated from white cells by the salting-out method. Polymerase chain reactions were performed by using primer sequences derived from published data. The amplification cycle was performed on a Perkin-Elmer Cetus 2400 Thermal Cycler with initial denaturation for 4 minutes at 94°C, followed by 35 cycles of 30 seconds at 94°C, 1 minute at 61°C, and 1 minute at 72°C, and finally by 7 minutes of extension at 72°C. For PON1-192, polymerase chain reaction products were digested with AlwI for 4 hours at 37°C, and the samples were electrophoresed in 3% agarose gels for 75 minutes at 60 V.

PON1-55 genetic polymorphism was determined in 50 FH patients and in 116 normolipidemic controls. For PON1-55 polymorphism, polymerase chain reaction products were digested with Hsp 92 II and electrophoresed in the same conditions as described above.

**Statistical Analysis**

For comparisons between baseline and posttreatment period values, statistical tests used were paired t test for normally distributed variables or a nonparametric Wilcoxon test for parameters with a skewed distribution. For comparisons between lipid traits and PON1 activity between genotype groups at baseline and after simvastatin therapy, a Mann-Whitney U test was performed. Spearman correlation coefficients were used to test the strength of the association between continuous variables. The χ² statistic was used to analyze associations in contingency tables.

**Results**

**Serum Lipid, Lipoprotein, Apolipoprotein and Lipid Peroxide Concentrations**

A major effect of simvastatin was to decrease serum cholesterol and LDL cholesterol concentrations by 19.9% and 26.3%, respectively (both P<0.001, Table 1). The decreases in serum apoB and LDL apoB were of a magnitude (20.5% and 21.1%, respectively; both P<0.001) similar to that of total and LDL cholesterol. There was also a significant decrease in serum triglycerides (15.6%, P=0.005). Conversely, simvastatin had no significant influence on VLDL lipid content, HDL cholesterol, apoAI concentrations, and LpAI and LpAII:AII particles.

Interestingly, the greatest change was observed in lipid peroxide concentrations, which were reduced by 37.3% after simvastatin therapy (P<0.001). This reduction was low but also significant when the lipid peroxide-to-LDL cholesterol ratio was considered (P=0.042). At baseline, there was a mild but significant correlation between lipid peroxide and LDL cholesterol concentrations (r=0.39, P=0.010). After therapy, correlation between both parameters was even more pronounced (r=0.64, P<0.001).

**PON1 Activity**

Remarkably, serum PON1 activity toward paraoxon significantly increased during treatment with simvastatin (12.3%, P=0.005; Table 2). Baseline PON1 activity was significantly
TABLE 3. Lipids, Lipoproteins, Apolipoproteins, Lipid Peroxides, and PON1 Activity Before (Basal) and After (Final) Simvastatin Therapy in 50 FH Patients Stratified by PON1-192 and PON1-55 Genotypes

<table>
<thead>
<tr>
<th>PON1-192 Polymorphism</th>
<th>PON1-55 Polymorphism</th>
</tr>
</thead>
<tbody>
<tr>
<td>QQ Homozygotes (n=31)</td>
<td>QQ Homozygotes (n=31)</td>
</tr>
<tr>
<td>Basal</td>
<td>Final</td>
</tr>
<tr>
<td>Serum cholesterol, mg/dL</td>
<td>309±40</td>
</tr>
<tr>
<td>Serum triglycerides, mg/dL</td>
<td>146 (106–178)</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dL</td>
<td>238±37</td>
</tr>
<tr>
<td>ApoB, mg/dL</td>
<td>145±23</td>
</tr>
<tr>
<td>LDL apoB, mg/dL</td>
<td>138±21</td>
</tr>
<tr>
<td>PON1 activity, U/L</td>
<td>118±49</td>
</tr>
<tr>
<td>Lipid peroxides, μmol/L</td>
<td>14.1±10.1</td>
</tr>
</tbody>
</table>

Values are mean±SD or mean (interquartile range).

*PON1 activity was significantly higher in R-carrier patients than in QQ homozygous FH patients for both measurements (P<0.001). †PON1 activity was significantly higher in LL homozygotes than in M-carrier patients (†P=0.007, ‡P=0.022).

lower in FH patients than in normolipidemic control subjects. This statistically significant difference disappeared after simvastatin therapy.

PON1 activity toward phenyl acetate (arylesterase activity) displayed a trend to higher values only after simvastatin therapy, which was not significant (P=0.166). Arylesterase activity was significantly lower in FH patients than in control subjects for both measurements (Table 2).

There were no significant differences in serum PON1 activity levels toward paraoxon between men and women for both measurements (168±87 U/L in men versus 169±109 U/L in women at baseline, P=0.917; 213±108 U/L in men versus 184±124 U/L in women after therapy, P=0.376). Conversely, a weak significant difference in arylesterase activity levels between men and women was found before therapy (100±27 U/mL in men versus 85±21 U/mL in women, P=0.046), which disappeared after simvastatin therapy (107±13 U/mL in men versus 96±21 U/mL in women, P=0.125). In the control group, mean arylesterase activities were similar in men and women (127±27 U/mL in men versus 134±31 U/mL in women, P=0.366).

A negative but not significant correlation between PON1 activity toward paraoxon and serum lipid peroxide concentrations was found before treatment (r=-0.05, P=NS). After simvastatin therapy, a significant negative correlation was observed between both parameters (r=-0.35, P=0.028). To answer the question of whether the increase in PON1 activity levels correlated with the decrease in serum peroxide concentrations, the difference of PON1 and lipid peroxide values after therapy from those obtained before treatment was calculated. A strong negative correlation between difference values of both parameters was observed (r=-0.64, P=0.001). Correlations between PON1 arylerase activity and lipid peroxides in both determinations were not significant.

Influence of PON1-192 and PON1-55 Polymorphisms

PON1-192 genotype frequencies in FH patients were compared with a previously reported genotype distribution in 310 randomly selected control subjects.11 PON1-192 genotypes in FH patients were distributed as follows: 31 (62%) QQ, 16 (32%) QR, and 3 (6%) RR. This distribution did not significantly differ from that of controls: 154 (49.7%) QQ, 123 (39.7%) QR, and 33 (10.6%) RR (P=0.239). FH patients were classified into 2 groups according to PON1-192 genotypes: homozygous patients for the Q allele (n=31) and those who had 1 or 2 R alleles (n=19). The influence of PON1-192 polymorphism on PON1 activity and on lipid traits that had significantly changed during treatment and the genetic influence on the response to simvastatin therapy were evaluated before and after simvastatin treatment (Table 3). No significant differences were found between the 2 genotype groups concerning serum concentrations of lipids and lipoproteins at baseline or after treatment. A similar trend (statistically or marginally statistically significant) in both genotype groups was observed with simvastatin therapy for all lipid parameters.

As expected, serum PON1 activities at baseline or after simvastatin therapy were significantly lower in the subset of the low-activity PON QQ genotype subjects than in R-carrier patients (P<0.001). No significant differences were observed between genotype groups in the therapeutic response of PON1 activity to paraoxon after simvastatin therapy (8.5% and 11.1% increase for QQ homozygous and R-carrier patients, respectively; P=0.28).

PON1-55 genotypes in 116 normolipidemic subjects were distributed as follows: 38 (32.7%) LL, 58 (50%) LM, and 33 (27.2%) MM. This distribution did not significantly differ from that of the FH patients: 13 (26%) LL, 31 (62%) LM, and 6 (12%) MM (P=0.294). Patients were classified in 2 PON1-55 genotype groups: LL homozygotes and M carriers. With the exception of serum triglycerides, a similar trend (statistically or marginally statistically significant) in both genotype groups was observed with simvastatin therapy for all parameters. There was no significant difference in the percentage of change for PON1 activity levels after therapy between the 2 genotype groups (12.7% for LL homozygotes and 9.5% for M carriers, P=0.440). FH patients who were homozygous for the L allele had significantly higher PON1 activity levels in both measurements than those carrying the M allele.

No statistically significant correlations between PON1 activity levels and HDL cholesterol, apoAI, or LpAI concen-
trations were observed in patients stratified by PON1-192 or PON1-55 genotypes, before or after simvastatin therapy.

Discussion

Human and animal studies strongly support the hypothesis that oxidative modification of LDLs plays a crucial role in the pathogenesis of atherosclerosis. Therefore, mechanisms preventing LDL oxidation appear to be antiatherogenic. In this respect, HDL-associated PON1 may be a major defense barrier against lipid peroxides from oxidized LDLs. In vivo, PON1 may directly act on lipid peroxides, or more likely, lipid peroxides are first transferred to HDL and then destroyed by PON1. Clearly, there is an obvious need to know whether environmental factors, such as diet or therapeutic factors, can influence serum PON1 activity or protein concentrations.

The findings of the present study lead to 2 major conclusions. First, serum PON1 activity toward paraoxon was considerably lower in FH patients without lipid-lowering therapy than in normolipidemic subjects. Simvastatin therapy appears to significantly increase PON1 activity to values closely similar to those of the control population. This increased PON1 activity was associated with a significant reduction of lipid peroxide concentration. On the other hand, whereas PON1 activity rose significantly after simvastatin therapy, HDL cholesterol concentration and apoAI as the major protein of HDL remained unchanged. Second, the therapeutic response of PON1 activity to simvastatin therapy was independent of PON1-192 and PON1-55 polymorphisms.

The significant low PON1 activity levels in FH patients compared with normolipidemic subjects found in the present study is consistent with the results of a previous study conducted in patients presenting heterozygous FH. We previously found that the prevalence of the low PON1 activity QQ genotype in 310 control subjects from our area was 49.7%, which was lower than that found in FH patients (62%). However, because our sample size was relatively modest for making effective genotype comparisons, it is difficult to entirely attribute the low PON1 activities in FH patients to genotype differences. Nevertheless, differences in the PON1-192 genotype frequencies between FH patients and controls were not statistically significant. In agreement with Mackness et al., the decrease in PON1 activity may be a consequence of some aspect of the disease.

A second coding region in the human PON1 gene, the Met/Leu55 polymorphism, seems to be associated with differences in PON1 concentrations and activities. Because there were no differences in the distribution of the Met/Leu55 genotype frequencies between FH patients and controls, the low PON1 activities in untreated FH patients cannot be attributed to the influence of the Met/Leu55 polymorphism.

The effects of lipid-lowering drugs (such as 2 fibric acid derivatives, bezafibrate and gemfibrozil) on PON1 activity levels were recently investigated, and no influence was found. The present study is the first report showing a significant increase in serum PON1 activity in FH patients treated with simvastatin, a widely used statin. Statins have proved to be extremely effective in lowering LDL cholesterol by reducing the cellular production of cholesterol. However, the mechanism of these agents may be more complex than originally thought. Among data suggesting that statins may decrease hepatic production of apoB-100 and alter the production of HDL by the liver or gastrointestinal tract, it has been recently proposed that simvastatin acts as an antioxidant in lipoprotein particles. Therefore, the hypothesis under consideration was that simvastatin might have antioxidant properties through its influence on PON1-HDL-associated particles.

Some studies have reported significant correlations between PON1 activity and lipid or protein content of HDL. In the present study, no statistically significant correlations between PON1 activity levels and HDL cholesterol, apoAI, or LpAI concentrations were observed in patients stratified by PON1-192 or PON1-55 genotypes in both determinations. In fact, despite its effects on serum PON1 activity, simvastatin at a dose of 20 mg daily was unable to change either HDL cholesterol and apoAI levels or LpAI and LpAI:AII particle concentration. These observations raise some interesting considerations. Although PON1 has been described as preferentially associated with HDL subfractions containing apoAI, the increase in PON1 activity under the influence of low-dose simvastatin therapy appears to be independent of HDL cholesterol and apoAI concentrations. Therefore, if simvastatin is assumed to have antioxidant properties, the latter are not due to changes in apoAI-containing lipoprotein concentrations, which may enhance PON1 activity. It has been suggested that serum PON1 activity may be associated with different species of HDL particles. In this respect, a population of HDL-containing apoJ has been described, which is physically associated with PON1 in HDL, with the constant apoJ-to-PON1 molar ratio being 8.2±2.1 in affinity-purified apo lipoproteins. It appears that apoAI is not associated with the majority of plasma apoJ HDL. Therefore, one explanation may be that simvastatin enhances the incorporation of PON1 in the specific apoJ-HDL subfraction, which does not contain apoAI. However, evidence is at this time too scarce to warrant speculation on this topic, given that there are also other plausible explanations in view of recently published data. PON1 activity has been shown to be reduced in the course of oxidative incubation with Cu2+-induced peroxidation of LDL. Oxidized LDL appears to inactivate PON1 through interactions between the enzyme-free sulphydral metabolism.
dryl group and oxidized lipids that are formed during LDL oxidation.29 Thus, PON1 may be partially inactivated in the presence of oxidative stress, as probably occurs in untreated FH patients. We show that simvastatin therapy was associated with a strong reduction in LDL cholesterol and in lipid peroxide concentrations and that PON1 activity was inversely correlated with lipid peroxide concentrations after simvastatin therapy. We also show that PON1 arylesterase, which is more representative of PON1 protein concentration,9 displayed only a nonsignificant trend to rise with therapy. Therefore, in view of recent data and the results of the present study, it seems reasonable to postulate that high-serum PON1 activity in treated FH patients is actually a consequence of a reduced oxidative stress elicited by simvastatin. Nevertheless, further studies are required to clarify the precise mechanism by which simvastatin therapy is associated with increased PON1 activity.

The data presented in the present study indicate that PON1-192 and PON1-55 genetic polymorphisms do not consistently affect the lipid, lipoprotein, apolipoprotein, and lipid peroxide concentrations, either at baseline or after simvastatin therapy. The results also show no significant influence of either PON1 polymorphism on the magnitude of changes in lipid parameters during treatment. However, because the sample size of each genotype group was relatively small, these results should be viewed with caution.

As expected, at baseline and after simvastatin therapy, serum PON1 activity levels were consistently lower in FH patients carrying the QQ genotype and the M allele than in those carrying the R allele and the LL genotype. Again, no differences were observed in the effect of simvastatin therapy on serum PON1 activity among genotype groups. This suggests that the simvastatin effect on PON1 activity is not mediated by PON1-192 or PON1-55 genotypes.

As previously described,8 serum PON1 activity levels toward paraoxon were unaffected by the sex of the individual. Conversely, arylesterase activity levels were slightly higher in men than in women, particularly at baseline. At present, it is difficult to explain this difference; however, the latter was not large, and the number of patients was too small to make effective comparisons. Furthermore, mean arylesterase activity was similar in men and women of the control group.

Uncertainties regarding whether PON1 activity, as measured by paraoxon hydrolysis, reflects the antioxidant capacity of the enzyme have recently been reported.28 Results involving the association of the high-activity R allele and coronary heart disease are also controversial. Thus, extensive research remains to be undertaken. Meanwhile, in view of the findings reported in the present study, we propose that simvastatin may have important antioxidant properties through increasing serum PON1 activity, perhaps as a consequence of reducing oxidative stress, by a mechanism independent of apoAI-containing lipoprotein concentration and without the influence of PON1-192 or PON1-55 genetic polymorphisms. Because this effect may be clinically significant, further studies concerning PON1 and cardiovascular disease prevention are clearly warranted.

Acknowledgments
This study was funded by a grant from Merck Sharp & Dohme SA. Marta Tomás was the recipient of a grant from the Fondo de Investigaciones Sanitarias (No. 99/9342). We thank Dave Mcfarlane for English revision of the manuscript.

References


Effect of Simvastatin Therapy on Paraoxonase Activity and Related Lipoproteins in Familial Hypercholesterolemic Patients
Marta Tomás, Mariano Sentí, Ferrán García-Faria, Juan Vila, Alex Torrents, Maribel Covas and Jaume Marrugat

Arterioscler Thromb Vasc Biol. 2000;20:2113-2119
doi: 10.1161/01.ATV.20.9.2113
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2000 American Heart Association, Inc. All rights reserved.
Print ISSN: 1079-5642. Online ISSN: 1524-4636

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://atvb.ahajournals.org/content/20/9/2113

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Arteriosclerosis, Thrombosis, and Vascular Biology can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Arteriosclerosis, Thrombosis, and Vascular Biology is online at:
http://atvb.ahajournals.org//subscriptions/