Mechanisms of HDL Reduction after Probucol

Changes in HDL Subfractions and Increased Reverse Cholesteryl Ester Transfer

Guido Franceschini, Marina Sirtori, Viola Vaccarino, Gemma Gianfranceschi, Laura Rezzonico, Giulia Chiesa, and Cesare R. Sirtori

Treatment with probucol, a widely used lipid-lowering agent, is associated with a significant reduction of high density lipoprotein (HDL) cholesterol levels, but with an apparently improved removal of cholesteryl esters from tissues (e.g., from tendon xanthomas). The effects of probucol (500 mg twice daily) on HDL subfraction distribution and cholesteryl ester transfer activity were tested in 12 patients with stable type II hyperlipidemia [low density lipoprotein (LDL) cholesterol > 180 mg/dl] after a placebo-controlled cross-over trial. Probucol significantly lowered total cholesterol (−13.8%), LDL cholesterol (−9.1%), and HDL cholesterol (−30%). By rate zonal ultracentrifugation, a marked reduction of HDL₂ cholesterol (−68%) was shown, whereas changes in HDL₃ were less significant (−21%). These findings were confirmed by polyacrylamide gradient gel electrophoresis, typically showing a reduction or disappearance of HDL₄ particles and the prevalence of particles in the HDL₃ range. Cholesteryl ester transfer from HDL to lower density lipoproteins was significantly increased (30%) in all patients. These findings suggest that, in addition to the well-documented in vitro changes (prevention of LDL oxidation and macrophage uptake), probucol characteristically modifies HDL particle distribution in vivo, and is associated with a significant increase of cholesteryl ester transfer activity. (Arteriosclerosis 9:462–469, July/August 1989)

Probucol is a widely used cholesterol-lowering drug, which reduces the cholesterol content of both low density (LDL) and high density (HDL) lipoproteins. This latter effect is particularly noteworthy since, generally, elevated HDL cholesterol levels are considered as an index of protection from arterial degenerative disease. In spite of this potentially harmful biochemical effect, probucol treatment has been associated with an apparently increased removal of cholesteryl ester stores, for example, from tendinous xanthomas. In this particular case, the reduction of the Achilles tendon thickness was directly related to the decrease of HDL cholesterol levels. Moreover, in numerous animal studies, administration of probucol was associated with a significant improvement of arterial lesions. In an attempt to explain the remarkable antiatherosclerotic activity of the compound in spite of the unfavorable lipoprotein changes, different hypotheses have been suggested. Prominent among these is the inhibition of oxidative changes of LDL resulting in the prevention of lipid accumulation in macrophages.

Since the major biochemical finding in probucol-treated patients is the dramatic reduction of HDL cholesterol and protein levels, it was decided to investigate whether this may be a specific target for the antiatherosclerotic activity of the compound. This study seemed to be particularly relevant in view of the lack of clear and definitive information on the activity of probucol on the HDL subfraction distribution, and the resultant very discrepant findings. In addition, our understanding of the dynamics of the HDL system has considerably improved in the last few years. The HDL subfraction distribution is linked to a continuous series of changes, involving the transformation of larger HDL into small HDL particles and vice versa by way of the hepatic lipase (HL), lecithin cholesterol acyltransferase (LCAT), and cholesteryl ester transfer protein (CETP) systems. By these mechanisms, HDL are capable of removing free cholesterol from tissues or from other lipoproteins, esterifying, and finally delivering cholesteryl esters to very low density lipoproteins (VLDL).

A controlled investigation was carried out in a selected group of type II hyperlipoproteinemic patients. We examined changes in the HDL subfraction distribution using a standardized rate zonal ultracentrifugation method and the activity of the CETP during active drug and placebo. The findings are consistent with a major effect of probucol on the HDL system, possibly related to the observed improvement of tissue cholesterol removal after treatment.

Methods

Study Subjects

Twelve patients (eight postmenopausal women and four men, ages 50.7 ± 9.4 years) with stable hypercholes-
terolemia (Fredrickson Type IIa) were selected for the study. Plasma lipid cutpoints were: LDL cholesterol level greater than 180 mg/dl and triglyceride levels less than 200 mg/dl. Five of the patients had familial hypercholesterolemia, which is that, several other family members with a similar condition; five had a sporadic form of the disease, with no affected member in the kindred; for two patients, family data could not be collected. All 12 patients had been known to our Lipid Clinic for 1 year or more; all were on a low fat (30% of calories) diet with a moderately elevated polyunsaturated/saturated ratio (1.2), which was maintained during the study. Ten patients had been on a prior drug treatment (fenofibrate, cholestyramine, or both), whereas one had been treated for some time with a soybean protein-based diet. All drug treatments and the soybean diet were stopped at least 8 weeks before the beginning of this study. All participating patients were fully informed of the modalities and end-points of the study, which was approved by our Internal Review Board, and the patients signed an informed consent form.

Protocol

Drug and placebo treatments were assigned according to a double-blind, cross-over protocol. Each patient received the active drug (Lurselle, Dow-Lepetit, Milano, Italy) in 0.5-g tablets twice daily and corresponding placebo tablets for two successive periods of 8 weeks separated by 4 weeks without treatment. Assignment of the sequence (placebo-probucol or probucol-placebo) was by random numbers. Before the start of the protocol, two fasting blood samples were collected 2 weeks apart for the determination of lipid, lipoprotein, and apolipoprotein levels (see below). Patients were to be excluded if the variation of total cholesterolemia, between the two samples, exceeded 20%.

During both active and placebo treatments, the patients were seen at 3-, 6-, and 8-week intervals; dietary compliance was evaluated by a registered dietitian; the patients were weighed, and blood pressure was monitored. Before the start of treatment, and at the 3- and 6-week intervals, limited lipid/lipoprotein determinations were carried out, whereas a complete lipoprotein fractionation, including HDL2 and HDL3 subtractions and determination of cholesteryl ester transfer activity, was carried out after 8 weeks of treatment.

Laboratory Procedures

Plasma total (TC), free cholesterol (FC), and triglyceride (TG) levels were determined by enzyme methodologies and were standardized within a WHO Quality Control program. The cholesteryl ester (CE) mass was calculated as (TC - FC) x 1.68. HDL cholesterol levels at 3 and 8 weeks were determined after precipitation of the apolipoprotein (apo)-B containing lipoproteins by dextran sulfate-MgCl2. Apo A-I, A-II, and B levels were determined by immunoturbidimetry. At time 0 as well as at the end of both placebo and probucol treatments (8 weeks), a complete lipoprotein fractionation was carried out by sequential ultracentrifugation. At these times, HDL subfractions were separated by rate zonal ultracentrifugation on sera maintained for not more than 1 week in the presence of 5.1 M NaBr, as previously described. The separated HDL subfractions were fully characterized in terms of flotation rate, serum concentrations, and lipid-protein composition. HDL particle size was analyzed by polyacrylamide gradient gel electrophoresis (GGE), according to the method of Nichols et al.

The net mass transfer of CE from HDL to lower density lipoproteins was determined essentially according to the methodology reported by Fielding et al. Plasma samples were incubated at 37°C under N2 in a shaking water bath in the presence of 0.15 M Na-iodoacetate as the LCAT inhibitor. The addition of the inhibitor, as previously reported for dithionitrobenzoic acid, does not influence the initial rate of CE transfer measured in incubated plasma. At progressive intervals (0, 15, 30, 60 minutes) pentuplicate plasma aliquots were treated with phosphotungstic acid-MgCl2 to precipitate VLDL and LDL; TC and FC were measured by an automated enzyme procedure in each supematant, and CE mass was calculated as described. The decrease of HDL-CE mass was linear during the 60-minute incubation (Figure 1), in agreement with data from other investigators. Regression lines were obtained for each plasma sample by plotting the HDL-CE values against the incubation time, and the net CE mass transfer from HDL to lower density lipoproteins was calculated as the slope of the regression line. The mean coefficients of variation for the method in our laboratory are: within run, 4.6% and between runs, 8.4%.

Statistically significant differences between the two treatments and between each treatment and the mean pretreatment values were analyzed by an analysis of variance, followed by Duncan's multiple range test. Regression analysis was performed by the least-squares method. Logarithmic transformation of TG values was carried out to normalize the skewed distribution usually observed in population studies.

Figure 1. Decrease in the high density lipoprotein (HDL) cholesteryl ester levels (nm/ml) (means±SEM) during in vitro incubation (min) of whole plasma from 12 hypercholesterolemic patients before (--) and after (—) treatment with placebo () and probucol ().
Results

All participating subjects satisfactorily concluded the study. Compliance to treatment, as determined by pill counting, was greater than 80% in all patients during the whole trial. No specific side effects were reported by any patient, and no significant changes in weight, blood pressure, hematological, or other biochemical parameters were noted.

When comparing the two sequences of treatment, that is, probucol followed by placebo and placebo followed by probucol (Figure 2), a remarkable stability of total cholesterol was noted during the placebo phase: a reduction from 8% (week 6) to 13.8% (week 8) was recorded during the active drug treatment. Triglyceridemia was only modestly affected by both treatments, whereas probucol caused consistent reductions in the HDL cholesterol levels (around -30%) as well as in total plasma apo A-I (-22.3%) (Table 1). Remarkably, in spite of a small but statistically significant reduction of LDL cholesterol (-9.1% at the end of treatment), apo B levels were essentially unchanged by probucol. Variations in an opposite direction were noted for TG in LDL and HDL (Table 1): LDL became relatively TG-enriched at the end of treatment (30.5%), with a concomitant significant decrease of plasma HDL-TG levels (-23.5%).

These lipoprotein/apolipoprotein changes led to significant alterations in the relative proportions of different components in plasma and in the separated lipoproteins. The apo A-I/A-II ratio was reduced from 1.09±0.33 to 0.88±0.99 after drug treatment (p<0.05), and similarly, the apo A-I/A-II ratio exhibited a significant fall (from 3.73±0.62 to 3.11±0.78, p<0.01). A slight, statistically significant reduction in the cholesterol transport capacity for HDL (HDL cholesterol/apo A-I) was noted (from 0.40±0.03 to 0.37±0.03, p<0.01), and the TG enrichment of LDL was also clearly documented by the reduced LDL TC/TG ratio (from 6.63±2.50 to 4.67±2.56, p<0.05). These same ratios were stable throughout the placebo treatment.

Table 1. Plasma Lipid, Lipoprotein, and Apolipoprotein Levels in 12 Hypercholesterolemic Patients Treated with Probucol and Placebo

<table>
<thead>
<tr>
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<th>Probucol</th>
<th>Placebo</th>
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<tr>
<td></td>
<td>Baseline</td>
<td>8 weeks</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>305.3±12.1</td>
<td>263.2±12.1†</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>139.9±17.4</td>
<td>131.3±27.2</td>
</tr>
<tr>
<td>VLDL-cholesterol</td>
<td>26.9±4.6</td>
<td>21.8±4.6</td>
</tr>
<tr>
<td>VLDL-triglycerides</td>
<td>87.9±17.0</td>
<td>68.1±21.7</td>
</tr>
<tr>
<td>LDL-cholesterol</td>
<td>229.3±13.8</td>
<td>208.3±12.6†</td>
</tr>
<tr>
<td>LDL-triglycerides</td>
<td>34.4±3.2</td>
<td>44.9±5.6</td>
</tr>
<tr>
<td>HDL-cholesterol</td>
<td>48.3±2.9</td>
<td>33.1±2.9†</td>
</tr>
<tr>
<td>HDL-triglycerides</td>
<td>22.6±4.4</td>
<td>17.3±3.7</td>
</tr>
<tr>
<td>Apolipoprotein A-I</td>
<td>121.7±5.5</td>
<td>88.7±7.3†</td>
</tr>
<tr>
<td>Apolipoprotein A-II</td>
<td>33.7±2.4</td>
<td>30.2±3.4</td>
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<tr>
<td>Apolipoprotein B</td>
<td>113.8±5.9</td>
<td>109.6±6.2</td>
</tr>
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</table>

Values are given as mg/dl (means±SEM).

*p<0.05, †p<0.01, ‡p<0.001 vs. baseline.

VLDL=very low density lipoprotein, LDL=low density lipoprotein, HDL=high density lipoprotein.

Examination of the HDL₂/HDL₃ subtraction pattern provided a clear and definitive evidence that the HDL₂ subtraction is dramatically reduced after probucol administration (Figure 3); the HDL₂ peak was essentially deleted in 9 of the 12 patients. This occurred independent of sex and of the relative plasma total and HDL cholesterol reductions. From the zonal ultracentrifugal profiles, a slightly reduced flotation rate of the HDL₃ subtraction after treatment was noted.

The mass, relative composition, and size of the HDL₂ and HDL₃ subfractions showed an excellent stability dur-
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Figure 3. Changes in distribution of the plasma high density lipoprotein (HDL) subfractions in two hypercholesterolemic patients treated with probucol. The rate zonal ultracentrifugation profiles from a female patient (top panel) and a male patient (bottom panel) show the dramatic effect of probucol on plasma HDL2 (right peak). The HDL3 concentration (left peak) increased in the woman and decreased in the man after treatment. Note the slight decrease of the HDL2 flotation rate after probucol in both patients. The HDL subfraction separations were carried out before (—) and after (- -) 8 weeks of drug treatment.

Table 2. Plasma Levels and Elution Volumes of HDL Subfractions In 12 Hypercholesterolemic Patients Treated with Probucol and Placebo

<table>
<thead>
<tr>
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<th>Probucol</th>
<th>Placebo</th>
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<tr>
<td></td>
<td>Baseline</td>
<td>8 weeks</td>
</tr>
<tr>
<td>HDL2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total mass (mg/dl)</td>
<td>66.7±11.3</td>
<td>20.7±5.4†</td>
</tr>
<tr>
<td>Associated cholesterol (mg/dl)</td>
<td>11.0±1.8</td>
<td>3.5±0.9†</td>
</tr>
<tr>
<td>Elution volume (ml)</td>
<td>7.82±0.06</td>
<td>7.61±0.09</td>
</tr>
<tr>
<td>HDL3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total mass (mg/dl)</td>
<td>298.5±22.8</td>
<td>262.5±20.5</td>
</tr>
<tr>
<td>Associated cholesterol (mg/dl)</td>
<td>38.0±2.6</td>
<td>29.8±2.2†</td>
</tr>
<tr>
<td>Elution volume (ml)</td>
<td>4.54±0.04</td>
<td>4.44±0.08</td>
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Values are the means±SEM. 
* p<0.01, † p<0.001 vs. baseline. 
HDL=high density lipoprotein.
Table 3. Composition of HDL Subfractions in 12 Hypercholesterolemic Patients Treated with Probucol and Placebo

<table>
<thead>
<tr>
<th></th>
<th>Probucol Baseline</th>
<th>Probucol 8 weeks</th>
<th>Placebo Baseline</th>
<th>Placebo 8 weeks</th>
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<tr>
<td></td>
<td>FC</td>
<td>CE</td>
<td>TG</td>
<td>PL</td>
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<tr>
<td>HDL₂</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>FC</td>
<td>4.3±0.4</td>
<td>20.7±3.4</td>
<td>5.3±2.5</td>
<td>28.1±2.5</td>
</tr>
<tr>
<td>CE</td>
<td>20.7±3.4</td>
<td>18.3±3.5</td>
<td>4.9±2.2</td>
<td>29.4±4.3</td>
</tr>
<tr>
<td>TG</td>
<td>5.3±2.5</td>
<td>4.9±2.2</td>
<td>4.9±2.0</td>
<td>28.6±3.1</td>
</tr>
<tr>
<td>PL</td>
<td>28.1±2.5</td>
<td>29.4±4.3</td>
<td>29.4±4.3</td>
<td>29.4±4.3</td>
</tr>
<tr>
<td>P</td>
<td>41.6±4.4</td>
<td>41.2±4.4</td>
<td>41.2±4.4</td>
<td>41.2±4.4</td>
</tr>
</tbody>
</table>

Values are the means±SD of % of weight. HDL=high density lipoprotein, FC=free cholesterol, CE=cholesterol esters, TG=triglycerides, PL=phospholipids, P=protein. *p<0.01, †p<0.001 vs. baseline.

Table 4. High Density Lipoprotein Particle Size in 12 Hypercholesterolemic Patients Treated with Probucol and Placebo

<table>
<thead>
<tr>
<th></th>
<th>Probucol Baseline</th>
<th>Probucol 8 weeks</th>
<th>Placebo Baseline</th>
<th>Placebo 8 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HDL₂a</td>
<td>HDL₂j</td>
<td>HDL₃a</td>
<td>HDL₃j</td>
</tr>
<tr>
<td>FC</td>
<td>100.5±2.2</td>
<td>85.3±1.8</td>
<td>99.1±0.9</td>
<td>84.1±0.6</td>
</tr>
<tr>
<td>CE</td>
<td>85.3±1.8</td>
<td>85.6±1.2</td>
<td>99.3±1.4</td>
<td>84.5±0.9</td>
</tr>
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High density lipoprotein (HDL) particle diameter (Å) was determined by polyacrylamide gradient gel electrophoresis. The values are the means±SD.

Figure 4. Polyacrylamide gradient gel electrophoretic profiles of high density lipoprotein (HDL) subfractions in six hypercholesterolemic patients treated with probucol. Two major populations of HDL particles, i.e., HDL₂a and HDL₃a, were identified in all the examined patients. The HDL₂a peak was dramatically reduced or deleted after 8 weeks of probucol treatment.

Figure 5. Changes in the net mass transfer of cholesteryl esters (nM/ml/hr) in 12 hypercholesterolemic patients treated with probucol. Plasma was incubated at 37°C in the presence of a lecithin cholesterol acyltransferase inhibitor; the decrease of the high density lipoprotein-cholesteryl ester mass was measured at 0, 15, 30, and 60 minutes, and the transfer was calculated as the slope of the regression line obtained for each sample. Transfer activity did not change during placebo treatment, and increased by 30% after 8 weeks of probucol treatment (p<0.001 vs. pretreatment).
tion with log VLDL-TG was still found, and the relationship with the TC/TG ratio in VLDL was maintained (Figure 6). In these latter cases, the slopes of the regression lines calculated from posttreatment values did not differ from pretreatment \((t=0.006\) and \(t=0.012\), respectively), indicating that the increased CE transfer activity is not a direct function of lipoprotein changes. The correlation between transfer activity and HDL-TG was also lost \((r=0.27)\), as was that with log VLDL-TG/HDL-TC (Figure 6). Finally, no correlation was found between the increase in transfer activity after probucol and the reduction of HDL-TC levels \((r=0.18)\).

Discussion

The major aim of this study was a characterization of the HDL system during probucol treatment. This appeared to be of particular interest in view of the unclear activity of this compound on HDL metabolism, particularly when considering that the reported reduction of HDL levels does not seem to be associated with any harmful effect on the vascular system. Indeed, there is clinical evidence suggesting that regression of xanthomas may be linked to HDL reduction.

The results obtained with two different separation techniques based on flotation rate and particle size confirm in a definitive way that the HDL₂ subtraction is more markedly affected by probucol administration, leading in some patients to an almost complete disappearance of HDL₂ from plasma. HDL₃ concentrations, by contrast, were not significantly influenced by probucol treatment.

These findings are, of course, not consistent with some previous data, which showed a more pronounced effect of probucol on the HDL₃ subtraction. These discrepancies may be due either to the use of unreliable separation methods, or to the selection of patients with different types of hyperlipoproteinemia. In the latter study, extrapolation of the data from the three type IIA patients shows a 74% reduction of HDL₃ levels after probucol, that is, close to those reported here. In our study, the effect of probucol on plasma HDL apolipoprotein concentrations was primarily on apo A-I, consistent with the dramatic reduction of apo A-I containing HDL₂ particles; in contrast, the apo A-II-rich HDL₃ were only marginally affected by active drug treatment. A predominant effect of probucol on the HDL₂ subtraction has also been reported by other authors.

Interestingly and most remarkably, probucol administration led to a highly significant increase of the CE transfer activity compared to the placebo treatment.
similar improvement in the CE transfer after probucol has been recently reported by Matsuzawa et al.\textsuperscript{39} in patients with a primary defect in the system. The net transfer of CE from HDL to lower density lipoproteins depends upon several variables: the amount of CETP in plasma,\textsuperscript{36,40} CETP binding to lipoproteins,\textsuperscript{41} the ratio between acceptor and donor lipoproteins,\textsuperscript{39} and the composition of these same lipoproteins.\textsuperscript{42} Finally, a plasma inhibitor of CETP has been identified.\textsuperscript{43} The increased transfer observed after probucol may result from a modification of one or more of these factors.

Confirming previous reports,\textsuperscript{35,42,44} the present findings indicate that the pretreatment transfer rate is directly related to several lipoprotein parameters, including the amount of TG-rich lipoproteins in plasma, their composition, and the ratio between VLDL and HDL. The increase in transfer activity after probucol is apparently independent from changes in VLDL levels and composition and is not related to parallel rises in the ratio between acceptor and donor lipoproteins (Figure 6). Furthermore, the two major effects of probucol on the HDL system, that is, the drop in HDL cholesterol and the increase in transfer activity, are not correlated. The effect of probucol on CE transfer would appear, therefore, not to be mediated by a modification in the plasma lipoprotein patterns. However, from the present data, a lack of competition by HDL particles as acceptors of the transferred CE, due to the markedly reduced levels, cannot be excluded, and the minor changes in HDL composition observed after treatment (Table 3), may alter the binding of CETP to these lipoproteins.\textsuperscript{41,45} To evaluate the substrate independent activity of CETP after probucol administration, in vitro experiments on isolated lipoproteins are planned.

Whatever the mechanism(s) responsible for the higher CE transfer rate, the result is the formation of TG-rich HDL\textsubscript{2} particles (an excellent substrate for HL\textsuperscript{17}), which are converted back to CE-poor HDL\textsubscript{3} (Table 3). The 30% increase of CETP activity was associated with a 30% fall of HDL cholesterol (partly due to a reduced content of CE in both HDL\textsubscript{2} and HDL\textsubscript{3}) and with a concomitant 23% decrease of apo A-I, possibly consequent to an impaired apolipoprotein synthesis.\textsuperscript{12,46} The lack of significant changes in HDL particle size, flotation rate, and composition are consistent with the hypothesis of an activation of the intravascular HDL metabolism leading to a reduction in the number of circulating HDL\textsubscript{2} particles. The improved CE transfer in plasma may also be associated with an enhancement of the HDL-mediated cholesterol efflux from cells, as demonstrated in cultured human skin fibroblasts incubated with probucol.\textsuperscript{47} Altogether, these findings may provide a biochemical ground for the reported association between reduced HDL cholesterol levels and xanthoma regression.\textsuperscript{5}

Some other concomitant biochemical changes were noted in the probucol-treated patients. The relative reduction in the cholesterol content of LDL without significant modifications of apo B levels is somewhat discordant with previous data, indicating a doubling of the LDL apo B removal rate after probucol treatment.\textsuperscript{48} These data were, however, not confirmed\textsuperscript{49} and, moreover, no change in LDL-B mass was reported in either study.\textsuperscript{12,48} The rise of LDL-TG content is of special interest and possibly of concern. In fact, increased LDL-TG has been linked to an impaired LDL receptor interaction in clinical hypertriglyceridemia.\textsuperscript{46} On the other hand, this alteration, which is characteristic of type IV patients and correctable with fibrate treatment,\textsuperscript{48} is generally associated with reduced LDL cholesterol levels. Whether an impaired receptor activity of LDL may be a consequence of probucol treatment is difficult to establish. Studies in an experimental homozygous condition have suggested that probucol may improve LDL catabolism, by mechanism(s) other than receptor interaction,\textsuperscript{49} possibly linked to the prevention of oxidative changes.\textsuperscript{9}

The major findings of this study support the hypothesis that, in addition to an antioxidant effect, probucol may modify plasma HDL metabolism, leading to reduced HDL cholesterol and HDL\textsubscript{2} levels, possibly associated with an improvement in the physiological process of tissue cholesterol removal.

Acknowledgments

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References


Index Terms: probucol • high density lipoprotein subfractions • cholesteryl ester transfer • hypercholesterolemia
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