Action of Atorvastatin in Combined Hyperlipidemia
Preferential Reduction of Cholesteryl Ester Transfer From HDL to VLDL1 Particles

Maryse Guerin, Taous S. Lassel, Wilfried Le Goff, Michel Farnier, M. John Chapman

Abstract—Combined hyperlipidemia (CHL) is characterized by a concomitant elevation of plasma levels of triglyceride-rich, very low density lipoproteins (VLDLs) and cholesterol-rich, low density lipoproteins (LDLs). The predominance of small, dense LDLs contributes significantly to the premature development of coronary artery disease in patients with this atherogenic dyslipoproteinemia. In the present study, we evaluated the impact of atorvastatin, a newly developed inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A (HMGCoA) reductase, on the cholesteryl ester transfer protein (CETP)–mediated remodeling of apolipoprotein (apo) B–containing lipoprotein subspecies, and more specifically, the particle subpopulations of VLDL and LDL in CHL. In parallel, we evaluated the atorvastatin-induced modulation of the quantitative and qualitative features of atherogenic apo B–containing and cardioprotective apo AI–containing lipoprotein subspecies. Atorvastatin therapy (10 mg/d for a 6-week period) in patients with a lipid phenotype typical of CHL (n=18) induced reductions of 31% (P<0.0001) and 36% (P<0.0001) in plasma total cholesterol and LDL cholesterol, respectively. In addition, atorvastatin significantly reduced VLDL cholesterol, triglycerides, and apo B levels by 43% (P<0.0001), 27% (P=0.0006), and 31% (P<0.0001), respectively. The plasma concentrations of triglyceride-rich lipoproteins (VLDL1, Sf 60 to 400; VLDL2, Sf 20 to 60; and intermediate density lipoproteins, Sf 12 to 20) and of LDL, as determined by chemical analysis, were markedly diminished after drug therapy (−30% and −28%, respectively; P<0.0007). Atorvastatin significantly reduced circulating levels of all major LDL subspecies, ie, light (−28%, P<0.0008), intermediate (−27%, P<0.0008), and dense (−32%, P<0.0008) LDL; moreover, in terms of absolute lipoprotein mass, the reduction in dense LDL levels (mean −62 mg/dL) was preponderant. In addition, the reduction in plasma dense LDL concentration after therapy was significantly correlated with a reduction in plasma VLDL1 levels (r=0.429, P=0.0218). Atorvastatin induced a significant reduction (−7%, P=0.0039) in total CETP-dependent CET activity, which accurately reflects a reduction in plasma CETP mass concentration. Total CETP-mediated CET from high density lipoproteins to apo B–containing lipoproteins was significantly reduced (−26%, P<0.0001) with drug therapy. Furthermore, CETP activity was significantly correlated with the atorvastatin-induced reduction in plasma VLDL1 levels (r=0.456, P=0.0138). Indeed, atorvastatin significantly and preferentially decreased CET from HDL to the VLDL1 subfraction (−37%, P=0.0064), thereby reducing both the levels (−37%, P=0.0001) and the CE content (−20%, P<0.005) of VLDL1. We interpret our data to indicate that 2 independent but complementary mechanisms may be operative in the atorvastatin-induced reduction of atherogenic LDL levels in CHL: first, a significant degree of normalization of both the circulating levels and the quality of their key precursors, ie, VLDL1, and second, enhanced catabolism of the major LDL particle subclasses (ie, light, intermediate, and dense LDL) due to upregulation of hepatic LDL receptors. (Arterioscler Thromb Vasc Biol. 2000;20:189-197.)

Key Words: cholesteryl ester transfer protein activity ■ HMGCoA reductase inhibitors ■ lipoprotein subspecies

Comoncomitent elevation of circulating levels of triglyceride-rich VLDL and cholesterol-rich LDL is recognized as being associated with an increased risk of premature coronary artery disease1 and is characteristic of subjects who exhibit a lipid phenotype typical of combined hyperlipidemia (CHL).2 An elevated plasma triglyceride concentration has long been linked to the prevalence of small, dense LDL particles.3 Moreover, a predominance of small, dense LDL in patients with a combined form of hyperlipidemia contributes significantly to the premature vascular disease characteristic of this atherogenic dyslipoproteinemia.4,5

It is now established that the plasma triglyceride level in the fasting state constitutes a key determinant of the LDL subclass profile6; indeed, plasma LDLs are derived principally from the intravascular lipolysis and remodeling of triglyceride-rich VLDL particles of hepatic origin.6 Packard...
and Shepherd\(^7\) have provided in vivo evidence that the subfraction profile and metabolic properties of LDLs are intimately related to the nature of their VLDL precursors. Thus, the particle size of nascent, hepatic VLDL represents a major factor in determining the extent to which VLDL particles are converted to LDL.\(^6\) Indeed, it has been proposed that the large, triglyceride-rich VLDL1 particle subfraction (Sf 60 to 400) generates the slowly metabolized, small, dense LDL subspecies, whereas large, light, and intermediate LDLs, which are rapidly cleared from the plasma, appear to result either from delipidation of IDL (Sf 12 to 20) or of VLDL2 (Sf 20 to 60), from direct secretion by the liver, or from a combination of these mechanisms.\(^7\)

Small, dense LDL particles typical of CHL result from an indirect mechanism involving an elevated rate of cholesteryl ester (CE) transfer from HDL to VLDL particles mediated by cholesteryl ester transfer protein (CETP).\(^8\) CETP plays a key role in the reverse cholesterol transport system by promoting the redistribution of neutral lipids, i.e., triglycerides and CEs, between plasma lipoprotein donor and acceptor particles.\(^9\) In normolipidemic subjects, CETP principally promotes the net transfer of CE mass from cardioprotective HDL to LDL.\(^10\) Among LDL subspecies, LDLs of intermediate density (d = 1.029 to 1.039 g/mL), which are known to possess an elevated binding affinity for the cellular LDL receptor\(^11\) and optimal apo B100 conformation,\(^12\) are preferentially targeted by CETP.\(^10\) Therefore, CEs are efficiently removed from plasma via a nonatherogenic pathway directly implicating the CETP-mediated CET mechanism. By contrast, patients displaying the CHL phenotype are characterized by an accelerated rate (2-fold) of CE mass transfer from HDL to VLDL and by the exchange of CEs between HDL and LDL in the absence of net CE mass transfer.\(^8\) It has been proposed that such abnormal CETP-mediated redistribution of CEs may underlie the formation of atherogenic, dense LDL subspecies in combined forms of hyperlipidemia as a consequence of the intravascular remodeling of CE-enriched LDL particles.\(^13\)

3-Hydroxy-3-methylglutaryl coenzyme A (HMGCoA) reductase inhibitors are highly effective in lowering both plasma cholesterol levels (up to 36%) and cholesterol-rich, LDL concentrations (up to 48%) in a dose-dependent manner in primary hypercholesterolemia.\(^14\)–\(^16\) The statins appear to affect the hepatic secretion of VLDL 21 and to promote intravascular remodeling of CE-enriched VLDL particles.\(^13\)

Patients with a combination of hypercholesterolemia and hypertriglyceridemia display a concomitant elevation of circulating levels of cholesterol and triglyceride. This phenotype, characterized by elevated levels of LDL cholesterol, VLDL cholesterol and triglyceride, and apo B, is termed CHL.\(^2\) Because there is, to date, no single genetic or clinical marker allowing identification of CHL patients, our classification is similar to that proposed by Arad et al\(^2\); i.e., a lipid profile including a triglyceride level >150 mg/dL and, as an additional criterion, an apo B concentration >130 mg/dL. It is relevant that the population study of Bruckert et al\(^26\) conducted in 3 towns in France, revealed that the 90th percentile for plasma triglyceride levels was equal to or >150 mg/dL and that the corresponding value for total cholesterol was equal to or >230 mg/dL. Furthermore, the European Atherosclerosis Society meeting on combined forms of dyslipidemia (Helsinki, Finland, 1998) reached a consensus that an apo B level ≥140 mg/dL is a key biological characteristic of this disorder.

Eighteen patients displaying a lipid phenotype typical of CHL, i.e., with fasting plasma levels of cholesterol <230 mg/dL and triglycerides >150 mg/dL, were selected for the study. One month before inclusion into the study, patients displayed a mean total plasma cholesterol level of 269 ± 34 mg/dL and a mean triglyceride concentration of 204 ± 59 mg/dL. Plasma cholesterol and triglycerides were verified on a second occasion (272 ± 33 and 216 ± 58 mg/dL for cholesterol and triglycerides, respectively) 15 days before the initial blood sampling at inclusion. All subjects exhibited levels of lipoprotein(a) <50 mg/dL. Patients were excluded if they displayed dysbetalipoproteinemia; diabetes mellitus; secondary causes of hyperlipidemia such as uncontrolled hypothyroidism, renal impairment, or nephrotic syndrome; or known liver or muscle disease. Other exclusion criteria included uncontrolled hypertension or any major cardiovascular event (myocardial infarction, severe or unstable angina pectoris, angiplasty, or cardiovascular surgery). None of the subjects was obese (body mass index <30 kg/m\(^2\)). The cohort was composed of 10 men and 8 postmenopausal women, aged between 35 and 75 years. Patients had ceased taking lipid-lowering drugs and signed an informed consent form 10 weeks before active treatment. This 10-week period before treatment corresponded to a dietary stabilization period (AHA Step 1 diet or equivalent), with a 6-week placebo period from weeks 6 to 0. At week 0, patients started a 6-week active period of treatment with atorvastatin (10 mg/d, once daily before dinner).
Blood samples for study of the lipoprotein profile and CETP activity were obtained after an overnight fast at the time of inclusion into the study and after 6 weeks of atorvastatin treatment. Blood was collected into sterile EDTA-containing tubes (final concentration 1 mg/mL), and plasma was immediately separated from blood cells by low-speed centrifugation at 2500 rpm for 20 minutes at 4°C.

Isolation and Chemical Analysis of Plasma Lipoprotein Subfractions

Subfractions of triglyceride-rich lipoproteins, ie, VLDL1 (Sf 60 to 400), VLDL2 (Sf 20 to 60), and IDL (Sf 12 to 20) were isolated by cumulative flotation after nonequilibrium density gradient ultracentrifugation with the use of a Beckman SW41 Ti rotor.27 The density of each plasma sample (2 mL) was increased to 1.118 g/mL by addition of dry, solid NaCl. The discontinuous density gradient was constructed with the use of a Buchler Autodensiflow as follows: 0.5 mL of an NaCl-NaBr solution of density 1.118 g/mL; 2 mL of plasma at density 1.182 g/mL; 1 mL of d = 1.0988 g/mL; 0.3 mL of d = 1.086 g/mL; 1.9 mL of d = 1.079 g/mL; 1.9 mL of d = 1.0722 g/mL; 1.9 mL of d = 1.0641 g/mL; and finally, 1.9 mL of d = 1.0588 g/mL. After centrifugation at 36,000 rpm for 2 hours at 23°C, the VLDL1 (Sf 60 to 400) fraction was collected at the meniscus of the tube in an aliquot of 1 mL. Each gradient was then overlayed with 1 mL of a background NaCl-NaBr solution of density 1.086 g/mL and recentrifuged at 36,000 rpm for 16 hours at 23°C. After this second ultracentrifugation, the VLDL2 (Sf 20 to 60) subfraction (0.5 mL) was collected at the meniscus of the tube. Finally, the IDL (Sf 12 to 20) fraction (0.5 mL) was obtained after a third ultracentrifugation at 36,000 rpm for 3 hours, 30 minutes at 23°C.

LDL and HDL subfractions were isolated from a second aliquot of plasma (3 mL) by isopycnic density gradient ultracentrifugation with a Beckman SW41 Ti rotor at 40,000 rpm for 44 hours at 15°C by a slight modification of the method of Chapman et al.28 Plasma density was increased to d = 1.21 g/mL by addition of dry, solid KBr. A discontinuous density gradient was constructed as follows: 2 mL of NaCl-KBr solution of density 1.24 g/mL; 3 mL of plasma adjusted to a background density of d = 1.21 g/mL; 2 mL of d = 1.063 g/mL; 2.5 mL of d = 1.019 g/mL; and finally, 2.5 mL of NaCl solution of density d = 1.006 g/mL. After centrifugation, gradients were fractionated from the top of the tube as follows: 5 LDL subfractions (LDL-1, d = 1.019 to 1.023 g/mL; LDL-2, d = 1.023 to 1.029 g/mL; LDL-3, d = 1.029 to 1.039 g/mL; LDL-4, d = 1.039 to 1.059 g/mL; and LDL-5, d = 1.050 to 1.063 g/mL) and 5 HDL subfractions (HDL2b, d = 1.063 to 1.091 g/mL; HDL2a, d = 1.091 to 1.110 g/mL; HDL3a, d = 1.110 to 1.133 g/mL; HDL3b, d = 1.133 to 1.156 g/mL; and HDL3c, d = 1.156 to 1.179 g/mL). All lipoprotein subfractions were collected by aspiration with a precision micropipette (Gilson) in aliquots of 0.8 mL, with the exception of the HDL2b subfraction, which was collected in an aliquot of 1.2 mL. We analyzed each HDL subfraction on nondenaturing polyacrylamide gels to determine their mean particle diameter. Our HDL subclasses isolated by density gradient ultracentrifugation are comparable to those previously described by Blanche et al.29 HDL2b (10.9 nm), HDL2a (9.1 nm), HDL3a (8.4 nm), HDL3b (8.0 nm), and HDL3c (7.7 nm).

Cholesterol and free cholesterol were quantified enzymatically using commercial kits (Boehringer Mannheim). CE mass was calculated as the sum of the masses of the individual components in each lipoprotein fraction. Total cholesterol and free cholesterol were quantified by a slight modification of the method of Guérin et al.10 Radiolabeled HDLs were obtained from the d2 > 1.063 g/mL fraction of a patient’s plasma by ultracentrifugation at 100,000 rpm for 3.5 hours at 15°C with a Beckman TL100 centrifuge. The d2 > 1.063 g/mL fraction was incubated overnight (18 hours) at 37°C in the presence of 4 μCi of [1,2,6,7-3H]cholesterol (specific activity 71 Ci/mmol) to allow endogenous lecithin:cholesterol acyltransferase to esterify the radioactive free cholesterol. After incubation, the density of the d2 > 1.063 g/mL fraction was increased to d2 = 1.21 g/mL by adding solid, dry KBr. HDL-containing, radioactive, esterified cholesterol was then isolated by centrifugation at 100,000 rpm for 5.5 hours at 15°C. Radiolabeled HDL preparations displayed a specific radioactivity that ranged from 8000 to 11,000 counts per minute per microgram CE. CET was determined after incubation of whole plasma from individual subjects at 37°C for 3 hours in the presence of radiolabeled HDL (equivalent to 1% of the total HDL-CE mass present in 1 mL of each subject’s plasma) and iodoacetamide (final concentration 1.5 mmol/L). After incubation, triglyceride-rich lipoproteins, ie, VLDL1, VLDL2, and IDL, were isolated by ultracentrifugation as described above. The total LDL fraction (d2 = 1.019 to 1.063 g/mL) was subsequently isolated by sequential ultracentrifugation at 45,000 rpm for 24 hours and the total HDL fraction (d2 = 1.063 to 1.21 g/mL) after ultracentrifugation at 45,000 rpm for 48 hours.

CETP-Dependent CET Assay

The CETP-mediated transfer activity in plasma was assayed by a slight modification of the method of Ahnadi et al30 by using an excess of an exogenous CE acceptor (d2 = 1.063 g/mL lipoproteins). Labeled HDL-CE (200 nmol) was combined with 800 nmol of VLDL/LDL-CE in the presence or absence of 50 μL of plasma used as a source of CETP. After incubation at 37°C for 3 hours, the density of the mixture was increased to d2 = 1.063 g/mL, and lipoproteins were isolated by sequential ultracentrifugation at 45,000 rpm for 24 hours. The radioactive content of the apo B–containing lipoproteins (d2 < 1.063 g/mL) and apo Al–containing lipoproteins (d2 = 1.063 g/mL) was then determined. The facilitated transfer of CEs from HDL to VLDL/LDL was calculated from the difference between the radioactivity transferred in the presence or absence of CETP.

Statistical Analysis

The effects of atorvastatin on plasma lipid levels, plasma concentrations and chemical compositions of lipoprotein subfractions, and CET from HDL to apo B–containing lipoproteins were determined by comparing these parameters at the time of inclusion into the study with those after 6 weeks of drug therapy by ANOVA using Student’s paired t test.

Results

Effects of Atorvastatin on Plasma Lipid and Apolipoprotein Levels

Plasma lipid and apolipoprotein levels before and after 6 weeks of atorvastatin treatment (10 mg/d) in CHL patients (n = 18) are shown in Table 1. At baseline, all subjects displayed plasma lipid levels characteristic of the CHL...
phenotype as defined in the Methods section above. After atorvastatin therapy, we observed significant reductions in both plasma total cholesterol (−31%, P<0.0001) and triglyceride (−27%, P=0.0006) levels. In addition, drug therapy significantly lowered plasma VLDL cholesterol (−43%, P<0.0001), LDL cholesterol (−36%, P<0.0001), and apo B (−31%, P<0.0001) concentrations. Moreover, no significant changes in HDL cholesterol or in apo AI concentrations were detected in atorvastatin-treated patients. Finally, atorvastatin treatment for 6 weeks did not induce significant variation in lipoprotein(a) levels.

**Effects of Atorvastatin on Plasma Lipoprotein Mass Distribution**

In this study, plasma lipoprotein particles were subfractionated by density gradient ultracentrifugation to yield multiple subspecies of triglyceride-rich lipoproteins (VLDL1, VLDL2, and IDL), LDL, and HDL. The mean reduction in total plasma triglyceride-rich lipoprotein concentration (VLDL1, VLDL2, and IDL) was 30% (P=0.0007) in CHL patients (259±15 and 181±10 mg/dL before and after treatment, respectively). Drug therapy significantly lowered (−37%, P<0.0001) plasma VLDL1 (Sf 60 to 400) levels (161±18 and 102±9 mg/dL before and after treatment, respectively; Figure 1). Furthermore, after lipid-lowering therapy, we observed reductions of 19% in plasma VLDL2 (Sf 20 to 60; 46±6 and 37±5 mg/dL before and after treatment, respectively) and of 20% in plasma IDL (Sf 12 to 20) levels (53±5 and 42±3 mg/dL before and after treatment, respectively). However, these latter changes did not attain statistical significance (P=0.0600 and P=0.0571 for VLDL2 and IDL, respectively). Interestingly, VLDL1 represented the predominant triglyceride-rich lipoprotein fraction in our CHL patients. Indeed, VLDL1 accounted for 62% and 56%, respectively, of total triglyceride-rich lipoprotein mass before and after atorvastatin treatment.

After drug administration, the mean plasma LDL concentration was reduced by 28% (429±20 and 301±17 mg/dL before and after treatment, respectively; P<0.0001). The density distribution of LDL subspecies mass is shown in Figure 2A. Before treatment, CHL patients displayed the asymmetric LDL profile typical of such combined forms of dyslipoproteinemia, in which the denser LDL subfractions, LDL-4 (d=1.039 to 1.050 g/mL) and LDL-5 (d=1.050 to 1.063 g/mL), predominate (the denser LDL subfractions, LDL-4 and LDL-5, accounted for 45% of total LDL concentration). After atorvastatin treatment, we observed significant reductions in the plasma concentrations not only of the light (LDL-1+LDL-2, −28%) and intermediate (LDL-3, −27%) LDL but also of the dense LDL (LDL-4+LDL-5, −32%) subfractions. Moreover, the most marked reductions in

**Table 1. Effect of Atorvastatin on Plasma Lipid and Apolipoprotein Levels in CHL Patients**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before Treatment</th>
<th>After Treatment</th>
<th>% Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol</td>
<td>267±35</td>
<td>184±23*</td>
<td>−31%</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>197±58</td>
<td>144±40*</td>
<td>−27%</td>
</tr>
<tr>
<td>VLDL cholesterol</td>
<td>46±15</td>
<td>26±6*</td>
<td>−43%</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>175±27</td>
<td>111±20*</td>
<td>−36%</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>46±8</td>
<td>46±6</td>
<td>0%</td>
</tr>
<tr>
<td>Apo B</td>
<td>144±18</td>
<td>99±17*</td>
<td>−31%</td>
</tr>
<tr>
<td>Apo AI</td>
<td>132±20</td>
<td>135±14</td>
<td>+2%</td>
</tr>
<tr>
<td>Lp(a)</td>
<td>31±7</td>
<td>32±8</td>
<td>+3%</td>
</tr>
</tbody>
</table>

Lp(a) indicates lipoprotein(a). All before- and after-treatment values are in mg/dL. Plasma lipid and apolipoprotein levels were determined before and after 6 weeks of atorvastatin (10 mg/d) treatment in CHL patients (n=18). Values are mean±SD. Analytical methods are described in the Methods section. *P<0.0006.
Effects of Atorvastatin on the Chemical Composition of Plasma Lipoprotein Subspecies

The mean weight chemical compositions of native lipoprotein subspecies (expressed as a percent of the free cholesterol, esterified cholesterol, triglyceride, phospholipid, and protein contents) are shown in Table 2. Analysis of triglyceride-rich lipoprotein subfractions revealed a significant effect of atorvastatin on the weight percent chemical composition of VLDL1 (Sf 60 to 400). Indeed, we observed an increase in the relative proportion of triglyceride associated with a reduction in that of CEs in the VLDL1 subfraction, thereby resulting in a significant reduction (~23%, \( P<0.005 \)) in the CE-to-TG ratio in these particles. By contrast, the chemical compositions of VLDL2 (Sf 20 to 60) and IDL (Sf 12 to 20) remained unchanged. Analysis of the composition of LDL subfractions failed to reveal an effect of drug therapy. Interestingly, a decrease in the ratio of CE relative to triglyceride was detected in all apo B–containing lipoprotein subfractions after drug therapy; statistical analysis with the nonparametric Wilcoxon test revealed that the trend in this modification of core lipid content was significant (\( P=0.0044 \)) in all VLDL, IDL, and LDL subfractions.

Among the HDL subspecies, we observed a significant reduction in the relative proportion of triglyceride in HDL2a (\( P=0.0319 \)), HDL3a (\( P=0.0284 \)), and HDL3b (\( P=0.0183 \)) subspecies after atorvastatin treatment. In parallel, the relative proportion of CEs was increased in HDL3a (\( P=0.0148 \)) and HDL3b (\( P=0.0211 \)). These modifications were associated with an increase in the CE-to-TG ratio in HDL2a (+29%, \( P=0.0019 \)), HDL3a (+30%, \( P=0.0098 \)), and HDL3b (+24%, \( P=0.0257 \)). Moreover, drug-induced elevations in the plasma concentration of CEs in both HDL2a and HDL3a subfractions (HDL2a-CE 8.7±3.2 and 11.2±2.7 mg/dL before and after treatment, respectively; \( P=0.0055 \)); and HDL3a-CE 12.7±2.6 and 14.9±3.8 mg/dL before and after atorvastatin, respectively, \( P=0.0277 \)) were detected. Considered together, these data suggest that the HDL2a, HDL3a, and HDL3b subfractions participate actively in the heteroxchange of CEs for triglyceride between HDL and VLDL on atorvastatin treatment in these patients. By contrast, the plasma concentration of triglyceride present in the HDL2b and HDL3c subfractions displayed significant reductions after lipid-lowering therapy (HDL3b triglyceride = 3.2±0.8 and 2.6±0.6 mg/dL before and after atorvastatin, respectively; \( P=0.0023 \); and HDL3c triglyceride = 2.2±0.6 and 1.9±0.6 mg/dL before and after atorvastatin, respectively; \( P=0.014 \)). These modifications appear to reflect alterations in intravascular neutral-lipid metabolism, possibly via CETP.

Effects of Atorvastatin on Exogenous Plasma CETP Activity

To determine whether atorvastatin exerted a modulating effect on plasma CETP levels, we employed an exogenous assay of CETP activity that accurately reflects plasma CETP concentration.\(^\text{30,31} \) The activity of CETP in the plasma of CHL patients (n = 16) was assessed before and after atorvastatin treatment by using an exogenous system containing HDL donor and VLDL/LDL acceptor particles isolated from normolipidemic plasma. After 3 hours of incubation, the mean transfer of CE radioactivity from HDL to an excess of exogenous VLDL/LDL acceptor was significantly reduced (~7%) by drug therapy (31.4±2.4% and 29.1±2.7% before and after treatment, respectively; \( P=0.004 \)). Thus, atorvastatin induced a significant reduction in CETP-dependent CET activity in CHL patients.

Effects of Atorvastatin on CET From HDL to Apo B–Containing Lipoproteins

Plasma CETP activity expressed as a percentage of radiolabeled CEs transferred from HDL to apo B–containing lipoproteins in CHL patients before and after atorvastatin...
treatment is shown in Figure 4. The mean transfer of radioactive CE was significantly reduced (−26%, P<0.0001) in plasma from CHL patients on drug therapy (30.6±7.7% and 22.6±7.9% before and after treatment, respectively). Furthermore, a reduction in the amount of radioactive CEs transferred from HDL ranged widely (6% to 55%) among our patients.

Table 3 shows the effect of atorvastatin on the transfer rate of CEs from HDL to individual apo B-containing lipoproteins in the plasma of CHL patients. After treatment, the rate of transfer of CEs from HDL to apo B-containing lipoproteins was significantly reduced (−21%, P=0.0079); this latter reduction resulted primarily from a net decrease in the rate of CE transfer from HDL to triglyceride-rich VLDL1 (−37%, P=0.0064), whereas rates of CE mass transfer from HDL to VLDL2 and IDL and of CE exchange between HDL and LDL were not significantly modified by drug therapy. Before treatment, large VLDL1 particles represented the major CE acceptor among triglyceride-rich lipoproteins in CHL patients. Thus, VLDL1 accounted for 50% of the total CE transferred from HDL to triglyceride-rich lipoproteins (ie, VLDL1, VLDL2, and IDL), whereas VLDL2 and IDL accounted for 20% and 30%, respectively. Since atorvastatin therapy preferentially regulated the rate of CE transfer from HDL to VLDL1 but did not modify that to VLDL2 and IDL, the VLDL1 subfraction did not remain the major CE acceptor among triglyceride-rich lipoproteins after drug therapy. Indeed, a similar proportion of CE was accepted by both VLDL1 (39%) and IDL (37%) in our atorvastatin-treated CHL patients. In addition, plasma CETP activity was significantly correlated with the atorvastatin-induced reduction in plasma VLDL1 levels (r=0.456, P=0.0138).

When the rate of CE transfer from HDL to apo B-containing lipoproteins is expressed relative to plasma lipoprotein mass concentration, then the relative capacity of each triglyceride-rich lipoprotein subfraction to accept CEs from HDL can be estimated. In CHL patients, IDL particles displayed the highest capacity to accept CEs from HDL

### Table 2. Effect of Atorvastatin on the Percentage Weight Chemical Composition of Lipoprotein Subspecies in CHL Patients

<table>
<thead>
<tr>
<th>Lipoprotein Subfractions</th>
<th>Chemical Component</th>
<th>FC</th>
<th>EC</th>
<th>TG</th>
<th>PL</th>
<th>Protein</th>
<th>CE/TG</th>
</tr>
</thead>
<tbody>
<tr>
<td>VLDL1 (Sf 60–400)</td>
<td>Before</td>
<td>4.1±1.2</td>
<td>13.5±2.4</td>
<td>61.3±4.0</td>
<td>10.2±1.8</td>
<td>10.9±2.2</td>
<td>0.22</td>
</tr>
<tr>
<td>After</td>
<td>4.3±0.7</td>
<td>10.8±1.5</td>
<td>64.3±2.9</td>
<td>9.9±1.2</td>
<td>10.6±2.0</td>
<td>0.17†</td>
<td></td>
</tr>
<tr>
<td>VLDL2 (Sf 20–60)</td>
<td>Before</td>
<td>5.7±0.7</td>
<td>23.2±2.9</td>
<td>41.1±4.3</td>
<td>15.4±1.5</td>
<td>14.7±1.0</td>
<td>0.56</td>
</tr>
<tr>
<td>After</td>
<td>5.4±0.9</td>
<td>19.6±4.8</td>
<td>45.7±8.6</td>
<td>14.6±2.0</td>
<td>14.6±1.3</td>
<td>0.43</td>
<td></td>
</tr>
<tr>
<td>IDL</td>
<td>Before</td>
<td>7.8±0.6</td>
<td>36.5±3.8</td>
<td>10.9±3.3</td>
<td>22.9±1.0</td>
<td>21.9±1.0</td>
<td>3.35</td>
</tr>
<tr>
<td>After</td>
<td>8.0±0.8</td>
<td>35.0±3.5</td>
<td>12.7±3.2</td>
<td>22.7±1.2</td>
<td>21.6±2.7</td>
<td>2.75</td>
<td></td>
</tr>
<tr>
<td>LDL-1 (d=1.019–1.023 g/mL)</td>
<td>Before</td>
<td>9.0±1.3</td>
<td>38.4±4.6</td>
<td>10.1±5.9</td>
<td>21.8±1.5</td>
<td>20.6±3.9</td>
<td>3.80</td>
</tr>
<tr>
<td>After</td>
<td>9.5±1.4</td>
<td>36.3±4.1</td>
<td>11.4±3.5</td>
<td>22.4±2.1</td>
<td>20.3±3.7</td>
<td>3.18</td>
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</tr>
<tr>
<td>LDL-2 (d=1.023–1.029 g/mL)</td>
<td>Before</td>
<td>8.6±0.9</td>
<td>40.2±2.5</td>
<td>7.4±2.9</td>
<td>22.3±1.0</td>
<td>21.5±2.4</td>
<td>5.43</td>
</tr>
<tr>
<td>After</td>
<td>8.8±0.9</td>
<td>39.0±2.8</td>
<td>8.5±3.6</td>
<td>22.3±1.6</td>
<td>21.4±3.7</td>
<td>4.59</td>
<td></td>
</tr>
<tr>
<td>LDL-3 (d=1.029–1.039 g/mL)</td>
<td>Before</td>
<td>7.4±1.0</td>
<td>39.5±1.7</td>
<td>8.0±2.0</td>
<td>22.0±0.9</td>
<td>22.9±2.1</td>
<td>4.94</td>
</tr>
<tr>
<td>After</td>
<td>7.6±0.8</td>
<td>38.6±2.3</td>
<td>8.5±3.4</td>
<td>22.5±2.9</td>
<td>22.8±2.9</td>
<td>4.54</td>
<td></td>
</tr>
<tr>
<td>LDL-4 (d=1.039–1.050 g/mL)</td>
<td>Before</td>
<td>6.9±0.8</td>
<td>39.6±2.6</td>
<td>7.1±2.2</td>
<td>21.7±1.1</td>
<td>24.7±2.3</td>
<td>5.58</td>
</tr>
<tr>
<td>After</td>
<td>7.0±0.8</td>
<td>38.8±1.9</td>
<td>7.3±2.3</td>
<td>21.8±1.3</td>
<td>25.0±2.6</td>
<td>5.31</td>
<td></td>
</tr>
<tr>
<td>LDL-5 (d=1.050–1.063 g/mL)</td>
<td>Before</td>
<td>6.5±1.0</td>
<td>36.0±4.3</td>
<td>8.0±2.6</td>
<td>21.4±2.0</td>
<td>28.1±2.8</td>
<td>4.50</td>
</tr>
<tr>
<td>After</td>
<td>6.7±1.8</td>
<td>34.5±4.6</td>
<td>8.2±2.7</td>
<td>21.8±2.4</td>
<td>28.8±3.6</td>
<td>4.21</td>
<td></td>
</tr>
<tr>
<td>HDL2b (d=1.063–1.091 g/mL)</td>
<td>Before</td>
<td>4.6±1.2</td>
<td>26.3±5.5</td>
<td>7.6±1.9</td>
<td>22.3±3.3</td>
<td>39.1±6.0</td>
<td>3.46</td>
</tr>
<tr>
<td>After</td>
<td>4.7±2.0</td>
<td>24.4±5.4</td>
<td>7.1±1.9</td>
<td>24.1±3.1</td>
<td>39.7±5.9</td>
<td>3.44</td>
<td></td>
</tr>
<tr>
<td>HDL2a (d=1.091–1.110 g/mL)</td>
<td>Before</td>
<td>3.2±1.4</td>
<td>18.6±2.8</td>
<td>7.0±1.8</td>
<td>24.4±2.8</td>
<td>46.8±4.3</td>
<td>2.66</td>
</tr>
<tr>
<td>After</td>
<td>3.2±1.4</td>
<td>20.6±3.5</td>
<td>6.0±1.4</td>
<td>26.4±2.4</td>
<td>43.8±4.5†</td>
<td>3.43†</td>
<td></td>
</tr>
<tr>
<td>HDL3a (d=1.110–1.133 g/mL)</td>
<td>Before</td>
<td>2.2±0.5</td>
<td>18.7±2.3</td>
<td>6.1±1.9</td>
<td>23.1±2.2</td>
<td>49.9±3.5</td>
<td>3.06</td>
</tr>
<tr>
<td>After</td>
<td>2.5±1.4</td>
<td>20.3±2.3*</td>
<td>5.1±1.3</td>
<td>24.3±2.0</td>
<td>47.8±2.7*</td>
<td>3.98*</td>
<td></td>
</tr>
<tr>
<td>HDL3b (d=1.133–1.156 g/mL)</td>
<td>Before</td>
<td>1.9±0.6</td>
<td>16.3±2.2</td>
<td>5.6±1.4</td>
<td>19.1±1.8</td>
<td>57.2±3.1</td>
<td>2.91</td>
</tr>
<tr>
<td>After</td>
<td>2.2±1.4</td>
<td>17.3±2.1*</td>
<td>4.8±1.1</td>
<td>19.8±1.7</td>
<td>55.9±2.7*</td>
<td>3.60*</td>
<td></td>
</tr>
<tr>
<td>HDL3c (d=1.156–1.179 g/mL)</td>
<td>Before</td>
<td>1.8±0.7</td>
<td>11.3±1.5</td>
<td>5.4±1.5</td>
<td>13.2±1.3</td>
<td>68.2±2.7</td>
<td>2.09</td>
</tr>
<tr>
<td>After</td>
<td>2.2±1.2</td>
<td>11.6±2.6</td>
<td>4.9±1.4</td>
<td>13.7±1.3</td>
<td>67.7±3.0</td>
<td>2.37</td>
<td></td>
</tr>
</tbody>
</table>

FC indicates free cholesterol; TG, triglyceride; and PL, phospholipid. Lipoprotein subfractions were isolated and chemical analyses performed in duplicate as described in the Methods section. Values are mean±SD. The chemical composition of each lipoprotein fraction was determined before and after 6 weeks of atorvastatin (10 mg/d) treatment in CHL patients (n=18).

*P<0.05, †P<0.005, and ‡P<0.0005 vs CHL patients before treatment.
We describe the effect of a novel HMGCoA reductase inhibitor, atorvastatin, on the modulation of plasma CETP activity and its relation to the quantitative and qualitative features of atherogenic apo B–containing and cardioprotective apo AI–containing lipoprotein subspecies in CHL patients. Atorvastatin significantly diminished the elevated transfer of CE from HDL to atherogenic, triglyceride-rich lipoproteins in these patients as a result of a preferential reduction in CE transfer from HDL to the larger, triglyceride-rich VLDL1 (Sf 60 to 400) particle subpopulation. Moreover, atorvastatin modified the atherogenic, dense LDL subspecies profile characteristic of CHL not only by inducing a major reduction in the plasma levels of the small, dense LDL subfractions (LDL-4, d = 1.039 to 1.050 g/mL and LDL-5, d = 1.050 to 1.063 g/mL; −32%) but also by decreasing circulating concentrations of both light (−28%) and intermediate (−27%) LDL subspecies. Moreover, in terms of absolute lipoprotein mass, the reduction in dense LDL levels (mean −62 mg/dL) was the most pronounced (Figure 2B).

In the present study, atorvastatin therapy (10 mg/d for 6 weeks) in patients displaying a lipid phenotype characteristic of CHL induced significant reductions in both plasma total cholesterol and triglycerides (31% and 27%, respectively) and equally in VLDL cholesterol (−43%) and plasma LDL cholesterol (−36%). Our findings are consistent with those previously reported by others.15,21,27,32–34 Equally, atorvastatin therapy induced significant modulation of both the quantitative and qualitative features of plasma lipoprotein subspecies. Total triglyceride-rich lipoproteins and LDL levels were significantly reduced (−30% and −28%, respectively) on drug administration. Interestingly, the reduction in the protein concentration of individual LDL subspecies was precisely equivalent to the reduction observed in the total plasma mass of the same subspecies. As apo B100 represents 90% or more of the protein moiety of LDL particles,35 then the observed variation in plasma LDL protein concentrations induced by atorvastatin should reflect a reduction in plasma LDL particle number. HMGCoA reductase inhibitors act primarily in the liver by inhibiting de novo cholesterol synthesis.36 The cellular regulatory response of these agents involves induction of the expression of the LDL receptor, which results in an increased hepatic catabolism of LDL particles. In addition, atorvastatin diminishes the concentration of circulating LDL particles through a reduction of their direct secretion by the liver.37 In a recent in vitro study, Mohammadi et al38 demonstrated that atorvastatin reduces apo B secretion as well as the number of apo B–containing lipoprotein particles produced by HepG2 cells. It has been proposed that atorvastatin alters the translocation of apo B into the lumen of the endoplasmic reticulum and thus, increases the amount of apo B degraded intracellularly.38 The normal assembly of apo B–containing lipoprotein particles is also impaired by the limited availability of endogenously synthesised cholesterol resulting from effective inhibition of intracellular cholesterol synthesis.

The subfraction profile and metabolic properties of LDL are intimately related to the nature of their VLDL precursors.7 Kinetic studies of apo B–containing lipoprotein metabolism have demonstrated that the presence of elevated plasma VLDL1 levels is intimately linked to the appearance of small, dense LDL.7 The large, triglyceride-rich VLDL1 (Sf 60 to 400) subfraction generates slowly metabolized, small, dense LDL subspecies, whereas light and intermediate LDLs appear to result from either direct secretion by the liver or by delipidation of VLDL2, IDL, or both. Under these conditions, the major reduction (−32%) in dense LDL concentrations observed after atorvastatin administration may result, at least partially, from a direct reduction (−37%) of VLDL1 levels and normalization of VLDL1 quality (Table 2). Equally however, statin-induced upregulation of the nonatherogenic,

**Figure 4.** Plasma CETP activity expressed as a percentage of total amount of labeled CE transferred from HDL to total apo B–containing lipoproteins (VLDL1, VLDL2, IDL, and LDL) determined in CHL patients (n = 16) before and after atorvastatin treatment (6 weeks, 10 mg/d). CETP activity assays were performed in duplicate as described in the Methods section. *P < 0.001.

(17.9 ± 6.3 μg CE transferred per h per mg lipoprotein mass) in comparison with that of VLDL1 (8.6 ± 2.3 μg CE transferred per h/ per mg lipoprotein mass, P = 0.0001) and VLDL2 (13.1 ± 5.3 μg CE transferred per h per mg lipoprotein mass, P = 0.01). Finally, atorvastatin therapy did not modify the relative capacity of triglyceride-rich lipoprotein subfractions to accept CEs from HDL.

### Discussion

We describe the effect of a novel HMGCoA reductase inhibitor, atorvastatin, on the modulation of plasma CETP activity and its relation to the quantitative and qualitative features of atherogenic apo B–containing and cardioprotective apo AI–containing lipoprotein subspecies in CHL patients. Atorvastatin significantly diminished the elevated transfer of CE from HDL to atherogenic, triglyceride-rich lipoproteins in these patients as a result of a preferential reduction in CE transfer from HDL to the larger, triglyceride-rich VLDL1 (Sf 60 to 400) particle subpopulation. Moreover, atorvastatin modified the atherogenic, dense LDL subspecies profile characteristic of CHL not only by inducing a major reduction in the plasma levels of the small, dense LDL subfractions (LDL-4, d = 1.039 to 1.050 g/mL and LDL-5, d = 1.050 to 1.063 g/mL; −32%) but also by decreasing circulating concentrations of both light (−28%) and intermediate (−27%) LDL subspecies. Moreover, in terms of absolute lipoprotein mass, the reduction in dense LDL levels (mean −62 mg/dL) was the most pronounced (Figure 2B).

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### TABLE 3. Effect of Atorvastatin on the Rates of CE Mass Transfer From HDL to Apo B–Containing Lipoproteins

<table>
<thead>
<tr>
<th>Lipoproteins</th>
<th>μg CE Transferred ( \cdot h^{-1} \cdot mL^{-1} )</th>
<th>% Change</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>VLDL1</td>
<td>Before 13.0±1.5, After 8.4±1.5</td>
<td>−37%</td>
<td>0.0064</td>
</tr>
<tr>
<td>VLDL2</td>
<td>5.1±0.5</td>
<td>−4%</td>
<td>0.7367</td>
</tr>
<tr>
<td>IDL</td>
<td>8.2±0.8</td>
<td>−1%</td>
<td>0.8832</td>
</tr>
<tr>
<td>LDL</td>
<td>22.3±2.0</td>
<td>−10%</td>
<td>0.3572</td>
</tr>
<tr>
<td>Total apo B–containing lipoproteins</td>
<td>48.8±4.1</td>
<td>−21%</td>
<td>0.0079</td>
</tr>
</tbody>
</table>

Rates of CE mass transfer were determined before and after 6 weeks of atorvastatin (10 mg/d) in CHL patients (see Methods). Values are mean ± SEM \((n=16)\). Apo B–containing lipoproteins are defined as total \(d<1.063 \text{ g/mL}\) lipoproteins and include VLDL1, VLDL2, IDL, and LDL subfractions. Lipoprotein subfractions, ie, VLDL1 (Sf 60–400), VLDL2 (Sf 20–60), IDL (Sf 12–20), and LDL \((d=1.019–1.063 \text{ g/mL})\) were isolated as described in the Methods section.
hepatic LDL receptor pathway may lead to enhanced catabolism not only of all major subclasses of LDL particles (ie, light, intermediate, and dense LDL) but also of their triglyceride-rich precursors. In this context, it is relevant that the effects of atorvastatin on the intravascular metabolism of triglyceride-rich lipoproteins and LDL occur independently of the modulation of lipoprotein lipase and hepatic triglyceride lipase activities in the rabbit model.30

Total HDL mass was not modified by atorvastatin. However, subtle modifications in the HDL subspecies profile were observed. Indeed, the relative proportion of HDL2a was significantly increased, whereas that of HDL3c decreased. In addition, the relative proportion of triglyceride in HDL2a, HDL3a, and HDL3b was significantly reduced, and those of CE increased in HDL3a and HDL3b on drug treatment. The quantitative and qualitative modifications of HDL subspecies are consistent with the reduction of plasma CETP activity observed after atorvastatin therapy. Indeed, HDL particles are actively involved in the heteroexchange of neutral lipids mediated by CETP. It has been previously demonstrated that after incubation, CETP may induce the production of small HDL particles (HDL3c) at the expense of larger HDL particles (HDL2a).40

Therefore, in the present study, the observed reduction in HDL3c concentration concomitant with an increase in HDL2a levels might reflect a modification in the intravascular neutral-lipid exchange reactions as a result of reduction in plasma CETP activity after atorvastatin therapy.

Interestingly, both triglyceride-rich lipoproteins (VLDL and LDL) and LDL displayed an equivalent relative capacity (54% and 45% of total radioactive CE transferred) to act as acceptors of radioactive CE from HDL in CHL patients, a finding consistent with our earlier data in patients presenting combined forms of hyperlipidemia.6 It is important to note that the transfer of radioactive CEs between lipoprotein subspecies is indicative of exchange and/or mass transfer reactions; indeed, net mass transfer of CEs with no reaction of exchange from HDL to VLDL occurs in plasmas from CHL patients.8,13 By contrast, no CE mass transfer is detectable from HDL to LDL, whereas radiolabeled CE transfer is observed, thereby suggesting that the only reactions of CE exchange occur between HDL and LDL in CHL.8,13 Consistent with these earlier observations, the rates of CE transfer from HDL to LDL reported in the present study represented CE exchange, as no variation in LDL-CE content was measurable after incubation of plasma at 37°C. Finally, atorvastatin therapy did not alter CE exchange between HDL and LDL in CHL patients.

The diminution in plasma CETP activity observed after statin therapy might result from a reduction in plasma CETP mass concentration. To verify this hypothesis, we employed an indirect assay in which plasma CETP concentration represented the limiting factor in CETP activity. This exogenous assay has been previously shown to accurately reflect plasma CETP mass.30,31 The CETP-dependent CET assay indicated that atorvastatin induced a minor (−7%) but significant reduction in plasma CETP concentration. Interestingly,Ahmadi et al demonstrated that simvastatin reduced plasma CETP concentration in a normolipidemic population. It is important to emphasise that simvastatin and atorvastatin are able to reduce plasma CETP activity through 2 distinct mechanisms. The simvastatin-induced reduction in plasma CETP activity appeared to result mainly from a reduction in plasma CETP mass.30 By contrast, in the present study, atorvastatin displayed only a minor effect on plasma CETP levels (−7%). However, the observed significant reduction in plasma CETP activity was related to the decrease in plasma VLDL concentration. Therefore, the observed reduction in plasma CETP activity after atorvastatin therapy appears to result mainly from a significant reduction in CE acceptor particle number. Statins are known to decrease cholesterol synthesis by competitively inhibiting HMGCoA reductase, the enzyme that catalyzes the rate-limiting step in the cholesterol biosynthetic pathway.36 Earlier studies showed that CETP gene expression is increased in response to dietary cholesterol or endogenous hypercholesterolemia.41 The DNA elements responsible for sterol-induced upregulation of the gene have been identified in the proximal CETP gene promoter.42 This positive sterol-response element might be involved in the minor lowering effect of atorvastatin on plasma CETP concentration through a reduction in CETP gene expression.

In conclusion, the reduction in plasma CETP activity induced by atorvastatin in CHL patients results at least in part from the marked decrease in plasma VLDL1 particle number. Moreover, we interpret our data to indicate that 2 independent but complementary mechanisms may be operative in the atorvastatin-induced reduction of atherogenic LDL levels in CHL: first, a significant degree of normalization of both the circulating levels and quality of their key precursors, ie, VLDL1, and second, enhanced catabolism of the major LDL particle subclasses (ie, light, intermediate, and dense LDL) due to upregulation of hepatic LDL receptors.

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References


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Maryse Guerin, Taous S. Lassel, Wilfried Le Goff, Michel Farnier and M. John Chapman

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