Effect of Atorvastatin on High-Density Lipoprotein Apolipoprotein A-I Production and Clearance in the New Zealand White Rabbit

Shirya Rashid, MSc; Kristine D. Uffelman, BSc; P. Hugh R. Barrett, PhD; Gary F. Lewis, MD, FRCP(C)

Background—HMG-CoA reductase inhibitors reduce the incidence of cardiovascular disease predominantly by their LDL-lowering effect. Recently, there has been great interest in the pleiotropic effects of statins, which appear to differ among the various agents in this class. Unlike other statins, atorvastatin exhibits a decline in its HDL-raising effect at higher doses in humans. Whether atorvastatin-mediated alterations in HDL turnover in vivo contribute to this effect has not previously been investigated. We therefore studied the effect of atorvastatin on HDL apoliprotein (apo) A-I production and clearance in normolipidemic male New Zealand White rabbits.

Methods and Results—Kinetic studies of HDL-apoA-I radiolabeled with 131I were performed in chow-fed rabbits after 3 weeks of atorvastatin treatment of 5 mg \( \cdot \) kg\(^{-1} \cdot \text{d}^{-1} \) versus placebo-treated rabbits (n=7). Our results showed a significantly (\( P<0.001 \)) more rapid clearance (~2-fold) of HDL apoA-I in atorvastatin-treated animals compared with the control group (0.121 ± 0.012 versus 0.061 ± 0.004 pools/h, respectively), accompanied by a lesser 48% increase in the apoA-I production rate (3.84 ± 0.38 versus 2.59 ± 0.41 mg \( \cdot \) kg\(^{-1} \cdot \text{h}^{-1} \), \( P=0.06 \)). Accordingly, plasma apoA-I levels in atorvastatin-treated animals declined significantly (\( P<0.05, n=8 \) animals) after 3 weeks of treatment (173.5 ± 1.8 mg/dL) from baseline values.

Conclusions—These data suggest that the effect on apoA-I levels observed with atorvastatin at higher drug doses in humans may be caused at least in part by enhanced HDL apoA-I catabolism, which is not entirely offset by a concomitant increase in apoA-I production. Whether this finding results from an effect of atorvastatin on HDL particle composition or on receptors involved in circulating HDL holoparticle clearance will require further study. (Circulation. 2002;106:2955-2960.)

Key Words: atorvastatin • hypercholesterolemia • apolipoproteins • lipoproteins
The production and clearance of HDL lipid and apolipoprotein moieties in vivo, in addition to alterations in plasma HDL levels per se, are important in determining the antiatherogenic effect of a drug therapy.5 There is limited information, however, regarding the effect of hypolipidemic agents on HDL production and clearance in the circulation. Therefore, in the present study, we investigated the effects of atorvastatin on the rate of HDL apoA-I production and clearance from the circulation of male New Zealand White (NZW) rabbits, an animal model in which LDL is the major apoB transporter of plasma cholesterol, as in humans. Kinetic studies of 131I-labeled HDL apoA-I were performed in wild-type NZW rabbits after 3 weeks of atorvastatin treatment and compared with a chow-fed plus drug vehicle control group.

Methods

Animals

NZW male rabbits (4 to 5 kg) were randomized into control or atorvastatin groups. Atorvastatin-treated rabbits received a daily standard chow diet14 containing 5 mg/kg atorvastatin and 3% coconut oil (C-1758, Sigma), a medium chain triglyceride (MCT), as drug vehicle (as previously described).15 Control rabbits received chow plus 3% coconut oil. After a 3-week treatment period, HDL turnover experiments were conducted, and plasma and HDL lipid and protein measurements were made in atorvastatin-treated (n=7) and control (n=7) animals. In addition, plasma and HDL measurements were made in another 16 animals (8 control and 8 atorvastatin-treated (5 mg·kg−1·d−1) before and after 3 weeks of treatment. All procedures followed were in accordance with the Animal Ethics Committee of the University Health Network.

Isolation and Radiolabeling of Rabbit HDL

HDL was isolated from rabbit serum by sequential ultracentrifugation as previously described.15 Approximately 1 to 3 mg of HDL protein from the control and atorvastatin-treated rabbits was iodinated by a modification of the iodine monochloride method of McFarlane (see Reference 16) using 250 μCi of 131I. An equal amount of unlabeled HDL from control or atorvastatin-treated rabbits was added to the radiiodinated HDL fractions as a cold carrier (1.52±0.16 mg HDL protein), and HDL tracers were washed at d=1.21/mL, 55 000 rpm, and 4°C in a 70.1-Ti rotor for 24 hours, followed by dialysis in Tris-EDTA buffer at 4°C.

HDL Turnover Study

The autologous tracers (containing 0.75±0.12 mg HDL protein and 10 to 15 μCi of 131I-HDL) obtained either from the atorvastatin-treated or control rabbits were injected simultaneously into the right marginal ear vein of the original donor after 3 weeks of treatment. Blood samples (2 to 3 mL) were obtained over the next 3 days (while the treatment regimen was continued) from a vein in the opposite ear. Blood samples (2 to 3 mL) were obtained over the next 3 days (while the treatment regimen was continued) from a vein in the opposite ear.

Isolation of HDL and ApoA-I for Radioactivity Counting

Radioactivity counting was performed as previously described.14,16 HDL was isolated (from 1 to 2 mL serum) by sequential ultracentrifugation as previously described.16 Aliquots of total serum and of the d<1.063-g/mL HDL, and d>1.21-g/mL serum fractions were taken to measure the proportion of 131I radioactivity found in each of these fractions.

ApoA-I was isolated from aliquots of dialyzed and delipidated HDL (300 μL) using 15% SDS-PAGE, as previously described.16 Radioactivity in each serum fraction and in the apoA-I band on the SDS gel was counted in a Beckman 5500 gamma counter. The apoA-I counts in the gel were taken as a percentage of the total gel counts, and the apoA-I counts in HDL were calculated from this.16 All radioactivity counts were corrected for the half-life of the isotope and adjusted back to the time of injection.

Laboratory Measurements

Cholesterol, triglycerides, phospholipids, cholesteryl ester, and protein were measured as described previously.14 ApoA-I concentrations were determined via electroimmunoassay using a goat anti-rabbit apoA-I antibody raised in our laboratory by a modification of methods previously described.17

Kinetic Analysis

The radioactivity die-away curves were analyzed with a 2-pool model using the SAAM II program (SAAM Institute), as previously described.16 The average coefficients of variation for apoA-I fractional catabolic rates (FCRs) were 15±2% and 14±2% for control and atorvastatin-treated rabbits, respectively. Production rate (PR) was computed as the product of FCR and apoA-I pool size. ApoA-I pool size, in turn, was derived from the following formula: (plasma volume (dL)×plasma apoA-I concentration (mg/dL))/body weight (kg), with the assumption that plasma volume is 3.28% of body weight.18

Statistics

Results are presented as mean±SEM. Unpaired t tests were performed to compare apoA-I FCR, apoA-I PR, lipid, and apoA-I values between control (chow-feeding drug vehicle) and atorvastatin-treated groups and to test differences in tracer composition. For the 16 animals that were studied before and after 3 weeks of either atorvastatin or placebo treatment, paired t tests were performed within each group to compare lipid and apoA-I levels at baseline versus after 3 weeks of treatment.

Results

Plasma and HDL lipid concentrations and plasma apoA-I concentrations in rabbits before and after 3 weeks of treatment are shown in Table 1. Treatment with atorvastatin resulted in a significant decline in total plasma cholesterol, cholesteryl ester, phospholipids, and apoA-I in comparison with pretreatment levels. In contrast, there was no significant change in plasma lipids or apoA-I in the control group after 3 weeks. HDL phospholipids increased significantly in both the control and atorvastatin groups, whereas HDL triglycerides increased to a significant extent only in the atorvastatin group.

Table 2 presents data for the rabbits that were used for the HDL turnover experiments. Mean lipid concentrations of the control rabbits and rabbits after 3 weeks of treatment with atorvastatin are shown. Plasma and non-HDL-cholesterol levels were both significantly lower in atorvastatin-treated animals than in the control group. The concentration of HDL cholesteryl was also significantly lower in the atorvastatin-treated group versus controls. The ratio of triglyceride to cholesterol was higher in HDL samples obtained from atorvastatin-treated rabbits than controls. The compositions of the HDL tracers isolated from serum after 2 weeks of either treatment with atorvastatin or chow feeding plus drug vehicle (control rabbits) are summarized in Table 3. The relative HDL masses of cholesterol, triglycerides, phospholipid, and protein were similar between the tracers. HDL tracers from atorvastatin-treated rabbits, however, tended to have a higher ratio of triglyceride to chole-
TABLE 1. Mean Lipid and ApoA-I Characterization of Control (n=8) and Atorvastatin-Treated (n=8) Rabbits Before and After 3 Weeks of Treatment

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Atorvastatin</th>
<th>% Change*</th>
</tr>
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<tbody>
<tr>
<td><strong>Plasma</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triglycerides</td>
<td>59.4±7.2</td>
<td>55.8±4.7</td>
<td>-6.0</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>48.5±4.9</td>
<td>43.8±6.3</td>
<td>-9.7</td>
</tr>
<tr>
<td>Cholesteryl ester</td>
<td>35.3±3.4</td>
<td>32.8±5.2</td>
<td>-7.0</td>
</tr>
<tr>
<td>Phospholipid</td>
<td>83.1±6.7</td>
<td>82.8±9.1</td>
<td>-0.3</td>
</tr>
<tr>
<td>ApoA-I</td>
<td>174.0±11.0</td>
<td>160.2±7.0</td>
<td>-7.9</td>
</tr>
<tr>
<td><strong>HDL</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triglycerides</td>
<td>11.7±0.8</td>
<td>13.1±1.3</td>
<td>11.7</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>13.6±1.0</td>
<td>15.4±1.9</td>
<td>12.8</td>
</tr>
<tr>
<td>Cholesteryl ester</td>
<td>10.9±0.7</td>
<td>12.5±1.6</td>
<td>15.1</td>
</tr>
<tr>
<td>Phospholipid</td>
<td>18.3±1.2</td>
<td>23.9±2.5</td>
<td>30.4†</td>
</tr>
</tbody>
</table>

Values are mg/dL, mean±SEM.
* % Change indicates the relative change in lipid concentrations in the control (chow-fed) or atorvastatin-treated animals above or below baseline values. There were no differences in baseline values between atorvastatin-treated and control animals.
†,‡,§, Significant intragroup difference between baseline and posttreatment values. †P<0.05; ‡P<0.01; §P<0.0001.

TABLE 2. Mean Lipid and Protein Characterization of Control (n=8) and Atorvastatin-Treated (n=8) Rabbits Used for the HDL ApoA-I Turnover Studies After 3 Weeks of Treatment

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Atorvastatin</th>
<th>% Difference*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Plasma</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triglycerides</td>
<td>51.7±2.9</td>
<td>49.3±8.9</td>
<td>-4.7%</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>32.1±2.8</td>
<td>19.6±2.3</td>
<td>-39.1%‡</td>
</tr>
<tr>
<td>Non-HDL cholesterol</td>
<td>22.0±2.3</td>
<td>13.3±1.3</td>
<td>-39.6%‡</td>
</tr>
<tr>
<td><strong>HDL</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triglycerides</td>
<td>11.4±1.0</td>
<td>13.0±2.5</td>
<td>13.8%</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>10.1±1.0</td>
<td>6.3±1.2</td>
<td>-38.0%†</td>
</tr>
</tbody>
</table>

Values are mg/dL, mean±SEM.
* % Difference indicates the relative difference in lipid concentrations between the atorvastatin-treated animals and the control, chow-fed animal.
†,‡,§, Significant difference between control and atorvastatin-treated animals.
†P<0.05; ‡P<0.01.

HDL versus control HDL tracers (≈2 to 1 versus ≈1.5 to 1, respectively, P=0.09).

The Figure illustrates the mean die-away clearance curves of radiolabeled HDL apoA-I in control chow-fed and atorvastatin-treated animals. The FCRs derived from the die-away clearance curves are shown in Table 4. There was a more rapid clearance of HDL apoA-I in atorvastatin-treated animals than in the control group, with a highly significant, 98% greater mean FCR with atorvastatin treatment. As stated above in the Methods section, the control and atorvastatin kinetic experiments were unpaired. We did not pair the experiments because we wished to inject the HDL tracers obtained from each control and atorvastatin-treated animal (2 weeks after initiation of treatment) back into the same donor animal; that is, we wanted to use autologous HDL tracers. Yet, despite the added interanimal variation induced by injecting the tracers into separate animals, we were able to detect a marked difference in the HDL apoA-I FCRs, making our results even more striking.

HDL apoA-I PRs for the control and atorvastatin-treated groups are shown in Table 4. There was a trend toward a higher (48%) HDL apoA-I PR in the atorvastatin-treated group versus controls.

### Discussion

In the present study, we show that atorvastatin enhances the clearance of HDL apoA-I from the circulation of normolipidemic NZW rabbits. Treatment with atorvastatin resulted in a highly significant (P<0.001) 98% enhancement in the FCR of HDL apoA-I, concomitant with a lesser increase in HDL apoA-I PR (48%, P=0.06), in comparison with control chow-fed animals. Accordingly, atorvastatin administration for 3 weeks resulted in a significant decline in plasma apoA-I levels (−19.4%, P<0.05).

Although there are exceptions,19 in most studies to date,3,7,9 atorvastatin has been found to exhibit a reduction in its HDL-raising effect with increasing drug dosage. In studies in humans with severe hyperlipidemas, Wierzbicki et al31,12 reported absolute reductions in HDL cholesterol levels after injecting the tracers into separate animals, we were able to detect a marked difference in the HDL apoA-I FCRs, making our results even more striking.

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atorvastatin treatment at the highest recommended drug dosage (80 mg/d). Nonetheless, in most studies, atorvastatin does not actually lower HDL levels. Several large clinical trials examining lipoprotein and apolipoprotein responses with atorvastatin have shown HDL cholesterol and apoA-I increases of 3% to 8% at lower doses of atorvastatin (10 to 20 mg), whereas at higher doses (40 to 80 mg atorvastatin), levels of HDL cholesterol and apoA-I are generally either minimally elevated or not significantly different from placebo. In general, the rise in apoA-I, the major protein component of HDL, tends to be smaller than that of HDL cholesterol. For example, in comparative human trials examining lipoprotein and apolipoprotein responses with atorvastatin, HDL cholesterol and apoA-I responses or HDL apoA-I turnover) after atorvastatin treatment. Although atorvastatin treatment did not result in a significant change in HDL cholesterol in these studies, it is difficult to compare the previous studies with the present one because of differences in drug dosage, length of treatment, and the ages and weights of the NZW rabbits (2 kg versus 4 to 5 kg in the present study) used among the studies. In the present study, we used a dose of 5 mg · kg⁻¹ · d⁻¹ of atorvastatin. Although higher doses of atorvastatin (up to 25 mg · kg⁻¹ · d⁻¹) have been used previously in the rabbit, the dose used in the present study is well tolerated by the rabbit and is not associated with toxicity and yet provides a respectable LDL cholesterol–lowering effect. We specifically selected this dose because a very high dose may not have been relevant to the effects of atorvastatin in humans.

In the present study, the more rapid clearance of HDL apoA-I occurring in the presence of a smaller increase in apoA-I production can explain the observed reduction in apoA-I levels in the atorvastatin-treated group. An increase in apoA-I PR has been relevant to the effects of atorvastatin in humans.

As observed in humans, in the rabbits in the present study, the apoA-I response to high-dose atorvastatin was more negative than the HDL cholesterol response 3 weeks after treatment (−4.2% change in HDL cholesterol and −19.4% change in apoA-I). Also, as has been widely observed in human trials, there was a marked heterogeneity in the HDL cholesterol response to atorvastatin. Although HDL cholesterol levels tended to be lower overall in atorvastatin-treated animals than controls, the difference was significant in the group in which the HDL turnover study was conducted but not in a separate group of animals in which pretreatment and posttreatment lipid values were compared.

Because of the many similarities in lipoprotein metabolism between rabbits and humans, the rabbit model has been widely used as a preclinical model to investigate the effect of statins on lipoprotein metabolism. The metabolism of lipoproteins in general, and HDL in particular, has also been well studied and characterized in this model. LDL is the major apoB cholesterol-transporting lipoprotein in rabbits and humans, and rabbits, like humans but unlike rodent and porcine models, express cholesteryl ester transfer protein (CETP), which plays a major role in lipoprotein metabolism. Two key differences between rabbits and humans is that the plasma CETP activity level in rabbits is 3 to 4 times higher than in humans, and although lipoprotein lipase activities are similar between the 2 species, hepatic lipase activity is greatly diminished in the rabbit.

Two previous studies in the normolipidemic chow-fed NZW rabbit examined HDL cholesterol responses (but not apoA-I responses or HDL apoA-I turnover) after atorvastatin treatment. Although atorvastatin treatment did not result in a significant change in HDL cholesterol in these studies, it is difficult to compare the previous studies with the present one because of differences in drug dosage, length of treatment, and the ages and weights of the NZW rabbits (2 kg versus 4 to 5 kg in the present study) used among the studies. In the present study, we used a dose of 5 mg · kg⁻¹ · d⁻¹ of atorvastatin. Although higher doses of atorvastatin (up to 25 mg · kg⁻¹ · d⁻¹) have been used previously in the rabbit, the dose used in the present study is well tolerated by the rabbit and is not associated with toxicity and yet provides a respectable LDL cholesterol–lowering effect. We specifically selected this dose because a very high dose may not have been relevant to the effects of atorvastatin in humans.

In the present study, the more rapid clearance of HDL apoA-I occurring in the presence of a smaller increase in apoA-I production can explain the observed reduction in apoA-I levels in the atorvastatin-treated group. An increase in apoA-I PR has been reported for other HMG-CoA reductase inhibitors, and as the coefficient of variation (CV) is the SD divided by the estimated FCR, expressed as a percentage. The CV is an estimate of the degree of precision of the FCR.

†‡ Difference between control and atorvastatin-treated animals. †P=0.06; ‡P<0.001.

**TABLE 4. FCRs and PRs of HDL ApoA-I From Control (n=7) and Atorvastatin (n=7) Experiments (Unpaired Experiments)**

<table>
<thead>
<tr>
<th></th>
<th>FCR, h⁻¹ (CV, %)</th>
<th>PR, mg · kg⁻¹ · h⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>0.064 (18.3)</td>
<td>2.95</td>
</tr>
<tr>
<td></td>
<td>0.058 (9.7)</td>
<td>2.60</td>
</tr>
<tr>
<td></td>
<td>0.053 (16.9)</td>
<td>3.92</td>
</tr>
<tr>
<td></td>
<td>0.061 (25.6)</td>
<td>1.94</td>
</tr>
<tr>
<td></td>
<td>0.045 (9.8)</td>
<td>1.08</td>
</tr>
<tr>
<td></td>
<td>0.074 (13.8)</td>
<td>1.52</td>
</tr>
<tr>
<td></td>
<td>0.076 (13.8)</td>
<td>4.11</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>0.077 (8.2)</td>
<td>2.21</td>
</tr>
<tr>
<td></td>
<td>0.090 (10.2)</td>
<td>2.88</td>
</tr>
<tr>
<td></td>
<td>0.105 (11.5)</td>
<td>3.56</td>
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<tr>
<td></td>
<td>0.134 (18.2)</td>
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<td></td>
<td>0.129 (17.4)</td>
<td>3.86</td>
</tr>
<tr>
<td></td>
<td>0.158 (19.5)</td>
<td>4.56</td>
</tr>
<tr>
<td></td>
<td>0.156 (13.1)</td>
<td>4.33</td>
</tr>
</tbody>
</table>

Mean ± SEM

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Atorvastatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± SEM</td>
<td>0.061±0.004</td>
<td>2.59±0.44</td>
</tr>
<tr>
<td></td>
<td>0.121±0.012†</td>
<td>3.84±0.41†</td>
</tr>
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</table>
demonstrated by recent in vitro studies, an increase in apoA-I mRNA levels accounts at least in part for the statin-induced increase in apoA-I production. More specifically, statins have been found to activate apoA-I promoter activity via activation of peroxisome proliferator–activated receptor-α, thereby stimulating apoA transcription and subsequently apoA-I mRNA levels. There is limited information, however, regarding the effect of HMG-CoA reductase inhibitors on HDL metabolism in vivo.

In a stable-isotope human study, Shaefer et al investigated the effect of pravastatin in 5 normolipidemic human subjects and in a patient with CAD. In contrast to the present study, the magnitude of the increase in apoA-I PR in that study was greater than the increase in apoA-I catabolism and resulted in a net increase in plasma HDL levels. It is tempting to speculate that the differing net effects of various statins on HDL levels could arise from differences in the balance between their stimulatory effects on apoA-I production and clearance from the circulation and should be determined in future studies. With respect to the HDL fraction, similar significant increases in HDL phospholipids (∼30%) in control and atorvastatin-treated rabbits after treatment may be explained by the incorporation of the MCT drug vehicle (3%) into HDL phospholipids (Table 1). In previous studies, supplementation of the diet with MCT (14%, 30 days) into HDL phospholipids resulted in a peak 2 to 1 in the atorvastatin group versus 1.5 to 1 in controls (P < 0.09 after 2 weeks of treatment, Table 3; P < 0.05 after 3 weeks of treatment, Table 2). An increase in HDL triglycerides has previously been demonstrated in response to atorvastatin treatment in humans; however, the mechanism of the atorvastatin-induced HDL triglyceride enrichment is not clear. Atorvastatin appears to inhibit CETP activity in humans, which should decrease HDL triglycerides, and fails to alter hepatic and lipoprotein lipase levels in the rabbit model, which should leave the HDL triglyceride content unchanged. Nonetheless, triglyceride enrichment of HDL has previously been shown to enhance HDL apoA-I catabolism in vivo, and combined with other drug-induced effects, could have contributed to the enhanced HDL apoA-I clearance in the present study. Although it has not been investigated, atorvastatin-induced upregulation of candidate HDL receptors involved in holoparticle HDL uptake by tissues such as liver and kidney remains a theoretical possibility.

Future studies are necessary to elucidate how receptors of HDL and HDL-modifying enzymes are involved in the atorvastatin-mediated effects on HDL kinetics and what the clinical implication of these effects is for the treatment of dyslipidemia in humans.

In the present study, we did not assess HDL cholesterol flux from peripheral tissues to the liver (i.e., reverse cholesterol transport) and therefore cannot exclude the possibility that an enhancement of reverse cholesterol transport by atorvastatin could contribute to its declining HDL-raising effect at higher drug doses. Such an enhancement of reverse cholesterol transport, if it were to occur, could be interpreted as being antiatherosclerotic and therefore protective against CAD. Nevertheless, the 2-fold atorvastatin-induced enhancement of HDL apoA-I clearance and the reduced apoA-I concentration speaks against enhanced reverse cholesterol transport being the exclusive mechanism of the declining HDL-raising effect of atorvastatin at higher drug doses.

Because apoA-I levels are inversely correlated with the risk of CAD, the increase in HDL apoA-I clearance and the accompanying reduction in apoA-I levels mediated by atorvastatin could diminish the antiatherosclerotic effect of atorvastatin. Nonetheless, we strongly caution against overinterpretation of the results of the present study and extrapolation to humans, for the following reasons: in addition to the fact that our observations may be species-specific, may not apply to humans, and were demonstrated in a normolipidemic group of animals, data from prospective randomized clinical trials investigating the effect of atorvastatin on cardiovascular end points indicate that at 80 mg/d, the maximum approved therapeutic dose of atorvastatin and also the dose at which both an HDL-lowering and/or minimal HDL-raising effects have been reported, beneficial effects on atherosclerotic cardiovascular disease have been demonstrated. Trials that directly compare the effect of atorvastatin versus other lipid-lowering agents on the incidence of cardiovascular disease will be necessary to indirectly determine the clinical significance of the differential HDL effect of the various agents in this class.

Acknowledgments

This work was supported by an Operating Grant from the Heart and Stroke Foundation of Ontario (Dr Lewis) and was funded in part by a research grant from Pfizer Canada (formerly Parke-Davis Canada) and by NIH grant RR-12609 and the Healy Medical Research Foundation. Shiya Rashid is a PhD student supported by the Heart and Stroke Foundation of Canada. Dr Lewis is a Career Investigator of the Heart and Stroke Foundation of Canada and holds a Canada Research Chair in Diabetes. Dr Barrett is a National Heart Foundation Career Development Fellow.

References

4. Nawrocki JW, Weiss SR, Davidson MH, et al. Reduction of LDL cholesterol by 25% to 60% in patients with primary hypercholesterolemia by approved therapeutic dose of atorvastatin and also the dose at which both an HDL-lowering and/or minimal HDL-raising effects have been reported, beneficial effects on atherosclerotic cardiovascular disease have been demonstrated. Trials that directly compare the effect of atorvastatin versus other lipid-lowering agents on the incidence of cardiovascular disease will be necessary to indirectly determine the clinical significance of the differential HDL effect of the various agents in this class.

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