# Effect of Atorvastatin on Apolipoprotein $B_{48}$ Metabolism and Low-Density Lipoprotein Receptor Activity in Normolipidemic Patients With Coronary Artery Disease

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**We aimed to examine postprandial dyslipidemia in normolipidemic patients with coronary artery disease (CAD) and the effects of treatment with an hydroxymethyl glutaryl coenzyme A (HMG-CoA) reductase inhibitor (atorvastatin). Subjects with angiographicaly established CAD were randomized to treatment for 12 weeks with 80 mg/d atorvastatin or placebo and the effects on markers of postprandial lipoproteins and low-density lipoprotein (LDL)-receptor binding determined. LDL-receptor binding was determined in mononuclear cells, as a surrogate for hepatic activity. Fasting levels of cholesterol ($P < .001$), LDL-cholesterol ($P < .001$), apolipoprotein (apo)$B_{48}$ ($P = .019$), remnant-like particle-cholesterol (RLP-C) ($P = .032$), and total postprandial apo$B_{48}$ area under the curve (AUC) ($P = .013$) significantly decreased with atorvastatin compared with placebo. Atorvastatin also significantly increased LDL-receptor binding activity ($P < .001$), and this was correlated with changes in fasting apo$B_{48}$ ($r = .80$, $P = .01$). We report that aberrations in chylomicron metabolism in normolipidemic CAD subjects are correctable with atorvastatin by a mechanism involving increased LDL-receptor activity. This effect may, in part, explain the cardiovascular benefit of statins used in clinical trials of CAD patients with normal lipid levels.**


THERE HAS BEEN intensive focus on the effects of hydroxymethyl glutaryl coenzyme A (HMG-CoA) reductase inhibitors on lowering plasma low-density lipoprotein (LDL)-cholesterol levels. Clinical trials have shown that improvements in plasma LDL levels are associated with retardation of atherosclerosis and reduction in coronary artery morbidity and mortality.[1,2] More recently, however, chylomicron remnants have been increasingly implicated in progression of atherosclerosis,[3-5] with elevated fasting remnant lipoprotein levels shown to independently predict clinical events in coronary artery disease (CAD) patients.[6]

Postprandial dyslipidemia has been found to be associated with endothelial dysfunction[7,8] an early indicator of atherogenesis.[9] Previous studies have shown that normolipidemic patients with coronary disease have elevated postprandial levels of intestinal triglyceride-rich lipoproteins (TRLs) and their remnants compared with healthy control subjects.[10-15] Elevated remnant lipoprotein levels have also been associated with coronary endothelial dysfunction,[16] with remnants shown to stimulate expression of proatherothrombotic molecules in endothelial cells.[17] Hence, the prevention and treatment of atherosclerosis merits pharmacotherapy targeted at regulating postprandial dyslipidemia.[18]

Possible mechanisms suggested for abnormal accumulation of intestinal lipoproteins postprandially in plasma are defective clearance via receptor-mediated pathways (eg, the LDL-receptor) and/or increased competition for high-affinity processes because of increased numbers of intestinally and hepatically derived particles postprandially.[18,19] HMG-CoA reductase inhibitors decrease cellular cholesterol synthesis and consequently reduce the hepatic production of very–low-density lipoproteins (VLDL) and increase expression of LDL-receptors.[20] These properties of statins suggest that they may be potential agents for regulating the plasma levels of atherogenic chylomicron remnants.

Atorvastatin is an HMG-CoA reductase inhibitor found to be effective in lowering fasting LDL-cholesterol and triglyceride levels.[21,22] Favorable effects of atorvastatin on postprandial lipoprotein metabolism have been reported in miniature pigs[23] and healthy normolipidemic human subjects.[24] Whether atorvastatin improves postprandial lipemia in normolipidemic patients with documented CAD has not yet been demonstrated.

In the present study, we used plasma triglyceride and apolipoprotein (apo) $B_{48}$, a specific marker for chylomicrons and their remnants, to investigate postprandial lipoprotein metabolism. We investigated whether the postprandial responses of CAD patients could be improved with atorvastatin and whether this effect involved alterations in LDL-receptor activity.

## SUBJECTS AND METHODS

### *Subjects*

We recruited 18 patients (15 men, 3 women) with angiographically documented CAD (1 or more vessels occluded) from the Cardiology Units at Royal Perth Hospital and Sir Charles Gairdner Hospitals, Perth, Western Australia. Subjects were excluded on the following criteria: total cholesterol $>$ 6.0 mmol/L, triglycerides $>$ 1.8 mmol/L, LDL-cholesterol $>$ 3.0 mmol/L, high-density lipoprotein (HDL)-cholesterol $<$ 1.0 mmol/L, body mass index (BMI) $>$ 29 kg/m$^2$, smokers, hypertension, E2 homozygosity, diabetes mellitus, gastrointestinal and renal disorders, endocrine and liver diseases, alcohol abuse, use of drugs known to influence lipid metabolism, and myocardial infarction or stroke within the last 6 months.

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*Submitted November 12, 2002; accepted May 23, 2003.*

*Supported by the National Heart Foundation of Australia, Royal Perth Hospital Centre for Excellence, and Pfizer.*

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*0026-0495/03/5210-0017$30.00/0*
*doi:10.1016/S0026-0495(03)00281-6*

### *Study Design*

CAD subjects in the intervention trial entered a run-in, stabilization phase of 8 weeks, after which they were randomized into a double-blinded, placebo-controlled trial of 12 weeks duration. Patients in the treatment arm were dose titrated from 10 mg to 80 mg atorvastatin daily for a 6-week period and then subsequently remained on 80 mg/d until completion of the 12 weeks. Patients in the placebo arm were administered a matching placebo regimen. Medication compliance was determined by tablet count and plasma lathosterol, a marker of cholesterol synthesis.[25] Clinical details including weight, BMI, waist:hip ratio, and blood pressure were measured at the beginning and end of the trial. Diet diaries were recorded throughout the study and analyzed using Diet 4 Nutrient Calculation Software (Xyris Software, Brisbane, Australia). The trial received approval by the Ethics Committees of Royal Perth Hospital and Sir Charles Gairdner Hospital, and all volunteers gave informed, written consent.

### *Oral Fat Test*

Postprandial tests were performed at the beginning and end of the intervention trial for the CAD patients. Patients were fasted for 14 hours and were advised to avoid alcohol and to have a light meal the day before the study. Blood samples were collected from an intravenous indwelling cannula placed in a forearm vein. After taking fasting samples, patients consumed an oral fat load that was prepared in the form of a milkshake containing 100 mL cream (47% fat wt/wt, 439.56 kcal per 100 g), 50 mL water, and 1 g chocolate powder. Venous blood samples were subsequently collected every 2 hours over a 10-hour period. Volunteers remained in the semirecumbent position throughout the oral fat test and were allowed to drink water only.

Blood samples were centrifuged at 1,500 $\times$ *g* for 10 minutes and the separated plasma protected from light. Plasma $apoB_{48}$, remnant-like particle-cholesterol (RLP-C), $apoB_{100,}$ lipids, glucose, and lathosterol:cholesterol ratio were determined. For all 6 plasma samples collected postprandially (including fasting sample), $apoB_{48}$ and triglyceride was determined. All analyses were performed within 24 hours of samples been taken.

### *Quantification of $ApoB_{48}$*

Chylomicrons and chylomicron remnants were isolated from plasma using a lipoprotein density fraction that ensured isolation of small dense chylomicron remnants (density $<$ 1.063 g/mL, 576,000 gh, Beckman SW41 rotor [Beckman Coulter, New South Wales, Australia]).[26] Briefly, apos from lipoprotein isolates were separated on a 5% to 20% sodium dodecyl sulfate (SDS) polyacrylamide gel and transferred to PVDF membranes. The membranes were incubated with an antibody to apoB (DAKO A/S, Glostrup, Denmark), and protein visualized using antirabbit immunoglobulin G (IgG) (horseradish peroxidase [HRP] conjugated) (Amersham, Buckinghamshire, UK) and enhanced chemiluminescence reagent (Amersham). Membranes were exposed to blue-light film (Amersham) and developed in an AGFA-Gevaert Rapidoprint X-Ray Developer (Septestraat, Belgium). $ApoB_{48}$ bands were identified and quantified by densitometry against purified $apoB_{48}$ protein of known mass. The mean intra- and interassay coefficient of variance for $apoB_{48}$ were each less than 4%.

Postprandial measures of plasma $apoB_{48}$ were calculated as the area under the curve (AUC) and the incremental-AUC.[27] Concentrations obtained over the 10-hour period after the fat load were used for these calculations. The incremental AUC (IAUC) was estimated as the difference between the area defined below the baseline concentration and the area under the plasma curve between 0 and 10 hours. The IAUC represents the increase in area after the response of the fat load above fasting concentrations. Postprandial plasma triglyceride AUC and IAUC were calculated similarly.

### *RLP-C Assay*

RLP-C was determined from plasma with a JIMRO-II (Japan Immunoresearch Laboratories, Takasaki, Japan) assay kit using an immunoseparation technique described by Nakajima et al.[28] Interassay coefficient of variation (CV) was less than 6%.

### *LDL-Receptor Activity in Human Monocytes*

LDL-receptor activity was measured according to the method of Roach et al[29] on the day of the postprandial assessment. Briefly, monocytes were isolated from fasting whole blood using a Ficoll separation method and frozen at −80°C in a background solution of 20% (vol/vol) sucrose. LDL-gold was then bound to the monocytes and total and nonspecific binding determined by measuring the absorbance of the bound gold when fixed with a silver stain enhancer (Amersham IntenseSE BL) using a Cobas Mira Autoanalyzer (Roche, Nutley, NJ). Interassay CV was less than 10%.

### *Other Biochemical Analyses*

Fasting total cholesterol and triglyceride were determined using enzymatic colorimetric methods on an Hitachi 917 Biochemical analyser (Hitachi, Tokyo, Japan) using Boehringer Mannheim reagents (Boehringer Mannheim, Mannheim, Germany). HDL-cholesterol was estimated after precipitation of apoB-containing lipoproteins (Boehringer Mannheim) and LDL-cholesterol derived from the Freidewald formula. Non–HDL-cholesterol was determined by subtracting HDL-cholesterol from total cholesterol concentrations. Plasma glucose was measured by a hexokinase reaction. $ApoB_{100}$ was measured by an immunonephelometric assay (Behring Diagnostics, Kingsgrove, NSW, Australia). Plasma lathosterol was measured using gas chromatography

**Table 1. Clinical Characteristics, Daily Nutrient Intake, and Fasting Glucose of CAD Patients Before and After Atorvastatin and Placebo Treatments**

| | Atorvastatin | | Placebo | |
|---|---|---|---|---|
| | Pre-treatment | Post-treatment | Pre-treatment | Post-treatment |
| BMI (kg/m$^2$) | 27.4 (1.34) | 27.4 (1.35) | 28.4 (1.53) | 28.5 (1.49) |
| Weight (kg) | 80.51 (4.59) | 80.64 (4.67) | 86.51 (5.57) | 87 (5.63) |
| Systolic blood pressure (mm Hg) | 117 (5) | 116 (4) | 126 (6) | 122 (5) |
| Diastolic blood pressure (mm Hg) | 72 (3) | 71 (2) | 75 (2) | 74 (2) |
| Fat (% energy) | 26.0 (1.9) | 26.9 (2.3) | 31.5 (2.9) | 30.5 (3.6) |
| Carbohydrate (% energy) | 45.6 (3.9) | 45.8 (3.6) | 44.2 (3.5) | 44.6 (4.5) |
| Protein (% energy) | 20.5 (1.0) | 20.1 (1.3) | 21.9 (1.2) | 21.0 (1.9) |
| Alcohol (% energy) | 7.6 (2.9) | 7.1 (2.8) | 2.5 (2.0) | 3.9 (2.6) |
| Fasting glucose (mmol/L) | 4.51 (0.13) | 4.40 (0.24) | 4.35 (0.16) | 4.28 (0.26) |

NOTE. Data expressed as mean (SEM).

**Table 2. Fasting Lipids, Apos, Remnant-Like Particle-Cholesterol and Apo $B_{48}$**

| | Atorvastatin | | Placebo | | |
|---|---|---|---|---|---|
| | Pre-treatment | Post-treatment | Pre-treatment | Post-treatment | *P* Value |
| Total cholesterol (mmol/L) | 4.52 (0.08) | 3.02 (0.16) | 4.86 (0.23) | 4.76 (0.21) | <.001 |
| Triglyceride (mmol/L) | 1.23 (0.20) | 0.95 (0.18) | 1.26 (0.23) | 1.17 (0.25) | .282 |
| LDL-cholesterol (mmol/L) | 2.71 (0.08) | 1.43 (0.17) | 3.19 (0.17) | 3.13 (0.19) | <.001 |
| HDL-cholesterol (mmol/L) | 1.28 (0.09) | 1.14 (0.07) | 1.11 (0.12) | 0.99 (0.1) | .905 |
| Non–HDL-cholesterol (mmol/L) | 3.24 (0.13) | 1.89 (0.19) | 3.74 (0.21) | 3.77 (0.22) | <.001 |
| Apol B-100 (g/L) | 0.82 (0.09) | 0.50 (0.05) | 0.91 (0.04) | 0.91 (0.04) | <.001 |
| Lathosterol ($\mu$mol/L) | 6.79 (1.40) | 1.83 (0.52) | 4.92 (0.69) | 5.75 (0.61) | <.001 |
| Lathosterol/cholesterol ($\mu$mol/mmol) | 1.50 (0.32) | 0.63 (0.21) | 1.05 (0.17) | 1.24 (0.16) | .001 |
| Remnant-like particle-cholesterol (mmol/L) | 0.28 (0.04) | 0.18 (0.02) | 0.25 (0.03) | 0.26 (0.03) | .032 |
| Fasting apolipoprotein $B_{48}$ (mg/L) | 17.01 (0.77) | 11.06 (1.07) | 15.11 (0.33) | 12.91 (0.63) | .019 |

NOTE. Data expressed as mean (SEM).

mass spectrometry.[30] Postprandial plasma cholesterol (TR13315; Trace Scientific, Melbourne, Australia) and triglyceride (TG-HR II; Waco Pure Chemical, Toyko, Japan) were determined using enzymatic colorimetric kits. Safety assessments of atorvastatin treatment on plasma liver (alanine transferase, asparate transferase, alkaline phosphatase) and muscle (creatine kinase) enzymes were measured every 2 weeks. Interassay CV for the above assays was less than 6.0%.

### *Statistical Analysis*

Data are expressed as mean (SEM) and log transformed to normalize skewed distributions. Data from the intervention trial were compared using general linear modelling adjusting for baseline differences between treatment and placebo groups. Correlations were examined by linear regression methods.

## RESULTS

Table 1 shows the clinical characteristics and dietary nutrient intake of CAD patients in the intervention study before and after treatment with atorvastatin or placebo. After randomization, CAD patients in treatment and placebo groups were well balanced, with no significant differences in BMI, weight, blood pressure, and fasting glucose. There were no significant within-group changes in BMI, weight, or blood pressure during the study. Average daily energy and nutrient intake of CAD patients (8,106.86 $\pm$ 399.52 kJ), did not change over the study period, as well as the proportion of energy intake from carbohydrates, protein, fat, and alcohol (see Table 1). Compliance with atorvastatin and placebo tablets was greater than 96%, with significant lowering in lathosterol levels found in the atorvastatin group alone. No adverse clinical effects or significant increases in liver or muscle enzymes were reported.

Age- and weight-matched control subjects had similar plasma concentrations of total cholesterol (4.68 $\pm$ 0.16 mmol/L), LDL-cholesterol (2.92 $\pm$ 0.12 mmol/L), HDL-cholesterol (1.30 $\pm$ 0.09 mmol/L), non–HDL-cholesterol (3.38 $\pm$ 0.11 mmol/L), as well as plasma triglyceride (0.97 $\pm$ 0.09 mmol/L) to the CAD subjects chosen for this study (Table 2). However, as reported previously by several other laboratories, control subjects also had lower fasting concentrations of chylomicrons determined as apo$B_{48}$ (9.5 $\pm$ 1.2 mg/L)[13] and a significantly lower incremental

**Table 3. AUC and IAUC for Plasma Triglyceride and Apo $B_{48}$**

| | Atorvastatin | | Placebo | | |
|---|---|---|---|---|---|
| | Pre-treatment | Post-treatment | Pre-treatment | Post-treatment | *P* Value |
| AUC triglyceride (mM · t) | 11.97 (1.67) | 9.39 (1.44) | 13.18 (2.07) | 14.3 (2.00) | .05 |
| IAUC triglyceride (mM · t) | 2.07 (0.40) | 2.22 (0.87) | 2.30 (0.35) | 3.90 (0.50) | .016 |
| AUC apolipoprotein $B_{48}$ (mg/L · t) | 148.96 (14.01) | 98.17 (14.93) | 106.61 (12.36) | 114.33 (15.39) | .013 |
| IAUC apolipoprotein $B_{48}$ (mg/L · t) | 30.48 (4.49) | 33.13 (7.86) | 23.23 (5.95) | 36.02 (9.09) | .286 |

NOTE. Data expressed as mean (SEM).
Abbreviations: AUC, area under the curve; IAUC, incremental area under the curve.

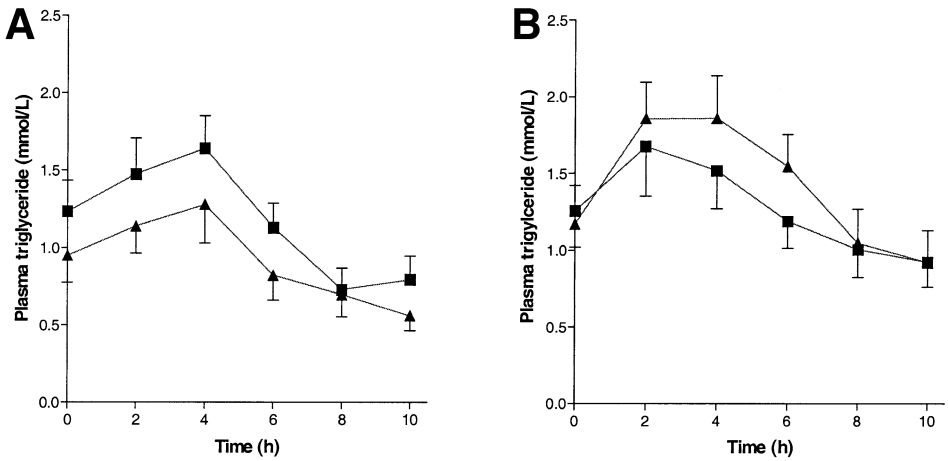



**Fig 1. Postprandial plasma concentrations of triglycerides before (■) and after (▲) 3 months treatment with (A) atorvastatin and (B) placebo in CAD patients. Mean and SEM is shown.**

area under the $apoB_{48}$ postprandial curve (data not shown).[10,11,14,15]

The fasting serum lipids, apos, RLP-C, and plasma lathosterol concentrations in CAD subjects before and after atorvastatin and placebo treatments are shown in Table 2. There was a significant decrease in the fasting plasma concentrations of $apoB_{48}$ (35%) and RLP-C (36%) with atorvastatin treatment. There were also significant decreases in serum total cholesterol (33%), LDL-cholesterol (47%), non–HDL-cholesterol (42%), $apoB_{100}$ (39%), and plasma lathosterol (73%) and lathosterol/cholesterol ratio (58%) with atorvastatin treatment compared with placebo. There were no significant changes in fasting serum triglyceride or HDL-cholesterol.

The AUC and IAUC for plasma triglyceride and $apoB_{48}$ in atorvastatin and placebo treatments are shown in Table 3. Compared with placebo, there was a significant decrease in plasma triglyceride AUC with atorvastatin treatment. The mean postprandial plasma triglyceride values before and after treatment in placebo and atorvastatin groups are shown in Fig 1. Figure 2 shows the postprandial curves for $apoB_{48}$ for atorvastatin and placebo groups. The AUC for $apoB_{48}$ also decreased significantly after atorvastatin therapy compared with placebo. This decrease was related to the significant decrease in $apoB_{48}$ values at baseline. However, the postprandial $apoB_{48}$ and triglyceride responses, reflected by the IAUCs, did not differ significantly between the atorvastatin and placebo groups.

LDL-receptor activity increased significantly ($P < .001$) with atorvastatin (177.2 ± 33.6 at baseline *v* 373.8 ± 43.1 LDL bound ng/mL after 3 months compared with placebo (244.1 ± 52.6 *v* 211.5 ± 56.9 LDL bound ng/mLprotein). Figure 3 summarizes the percentage changes in the postprandial AUC for triglyceride and $apoB_{48}$ between the atorvastatin and placebo groups, as well as the changes in LDL-receptor activity. While atorvastatin decreased postprandial triglyceride and $apoB_{48}$ AUC by 18% and 22% ,espectively, LDL-receptor binding activity increased by 218% with atorvastatin treatment.

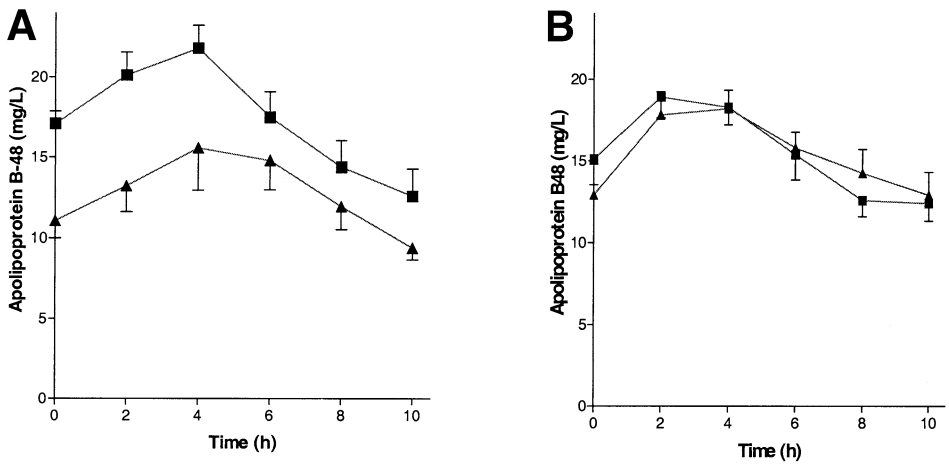
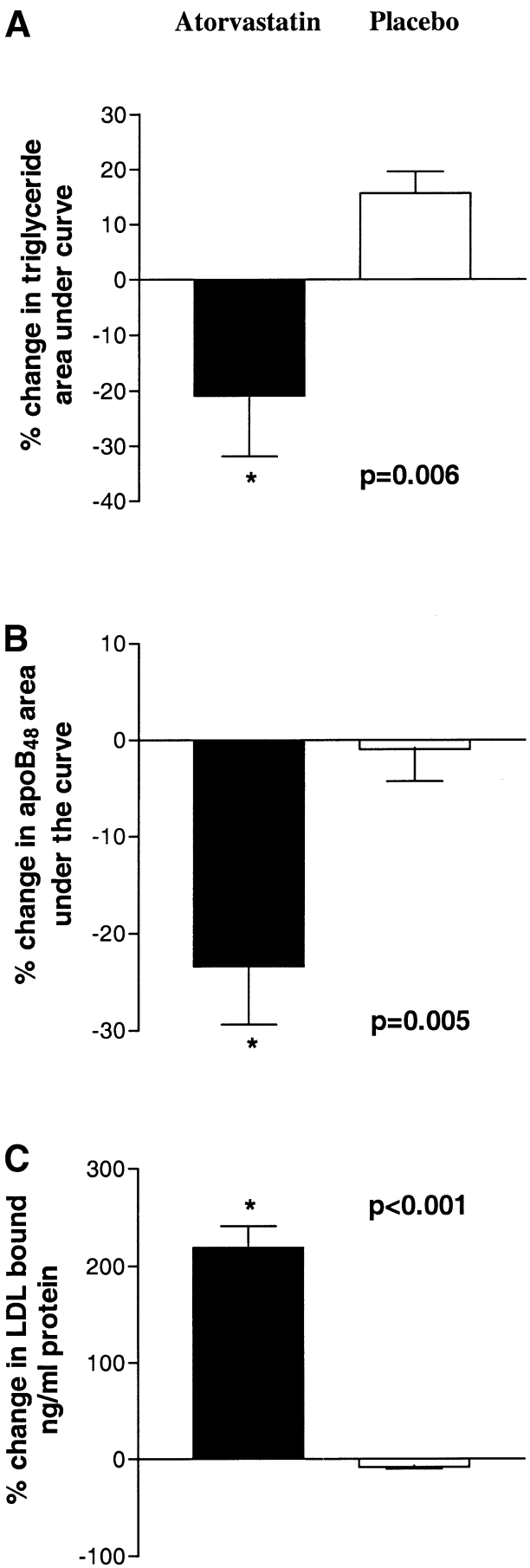



**Fig 2. Postprandial plasma concentrations of apolipoprotein $B_{48}$ before (■) and after (▲) 3 months treatment with (A) atorvastatin and (B) placebo in CAD patients. Mean and SEM is shown.**




Overall, changes in fasting $apoB_{48}$ levels were significantly associated with changes in fasting RLP-C levels ($r = .74$, $P = .018$) and LDL-receptor activity ($r = .63$, $P = .006$). A change in LDL-receptor activity was also significantly associated with changes in total $apoB_{48}$ AUC ($r = .79$, $P = .008$). Changes in fasting lathosterol/cholesterol ratio were associated with changes in fasting LDL-cholesterol ($r = .86$, $P < .001$) and $apoB_{100}$ concentrations ($r = .81$, $P = .003$). Within the atorvastatin group alone, changes in LDL-receptor activity remained significantly associated with the changes in fasting $apoB_{48}$ levels ($r = .80$, $P = .01$) and total $apoB_{48}$ AUC ($r = .87$, $P = .003$) (see Fig 4).

## DISCUSSION

The results of the present study demonstrate that treatment with atorvastatin decreased fasting markers of intestinal lipoproteins ($apoB_{48}$ and RLP-C), as well as total postprandial $apoB_{48}$ AUC and increased LDL-receptor activity in normolipidemic subjects with CAD.

Having confirmed increased concentrations of fasting chylomicron and postprandial dyslipidemia in the CAD patients, we investigated the putative effect of an agent known to upregulate pathways for postprandial lipoprotein metabolism.[20] To date, one other study has reported the effect of a statin in normolipidemic CAD patients, with a focus on the effect of simvastatin on postprandial and fasting triglyceride and the third complement component (C3).[31] Although previous studies have found atorvastatin to be effective in lowering triglyceride,[31] the reduction in fasting triglyceride in this study did not reach significance. However, like Halkes et al,[32] we report a decrease in the both total and incremental AUC for triglyceride in the statin-treated group compared with placebo. Lipase activities were not investigated in this study, but comparison of lipoprotein lipase and hepatic lipase activities found no differences between a smaller group of the CAD patients and healthy controls used in the present study (Dane-Stewart, 1998, unpublished data). We have, however, expanded on the work of Halkes et al with the measurement of $apoB_{48}$ postprandially and fasting markers of lipoprotein metabolism. On the findings of the latter, it is possible that an enhancement of lipoprotein particle kinetics independent of the lipolytic cascade may have been responsible for the improvement in postprandial triglyceride metabolism.

A significant decrease in the markers for chylomicrons and their remnants ($apoB_{48}$ and RLP-C) with atorvastatin indicates a lowering of the levels of these proatherogenic particles. We have previously shown that the fasting plasma concentration of $apoB_{48}$ may predict the postprandial response.[33] In agreement with this, we found a reduction in fasting $apoB_{48}$ followed a reduction in the total $apoB_{48}$ postprandial response. Measurement of LDL-receptor activity showed an increase in binding activity, which correlated with the reduction in plasma $apoB_{48}$ within the atorvastatin group. The changes in LDL-receptor activity together with reductions in $apoB_{48}$, as well as RLP-C, strongly suggests the decrease in the fasting levels of intestinal

**Fig 3. Summary of the percentage changes in (A) triglyceride, (B) $apoB_{48}$ area under the postprandial curves, and (C) LDL-receptor expression after 3 months of atorvastatin (■) and placebo (□) treatment. Mean and SEM is shown.**

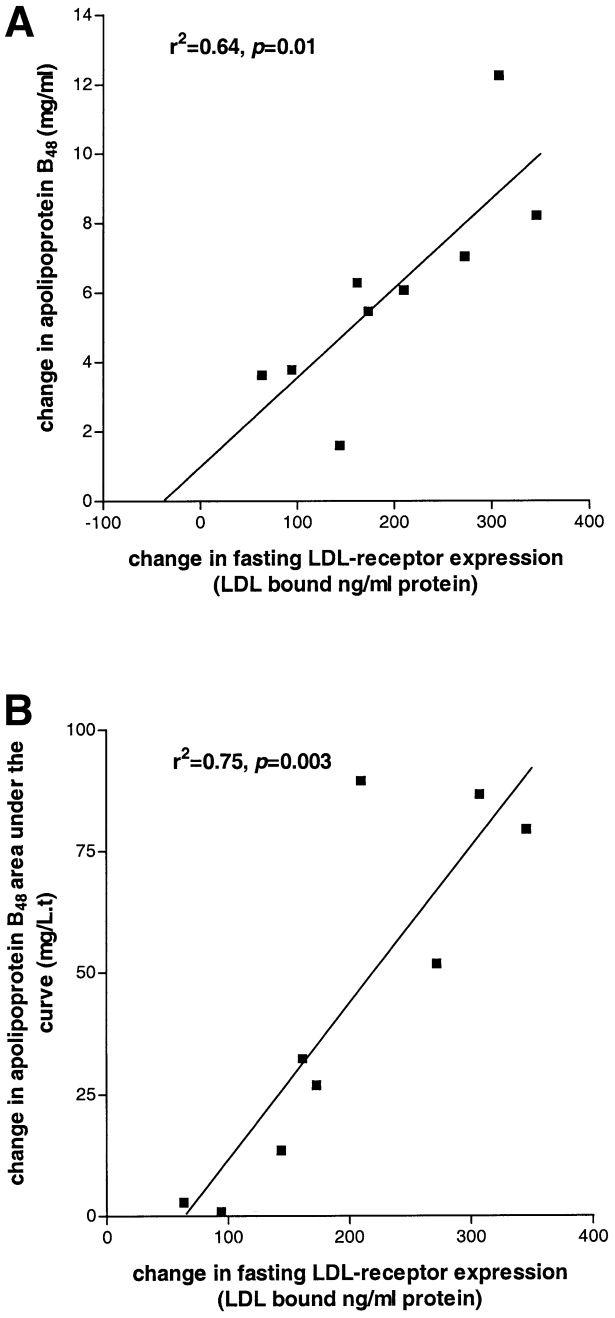



**Fig 4. Correlation between the changes in LDL-receptor expression and (A) fasting $apoB_{48}$ and (B) $apoB_{48}$ area under the postprandial curve after 3 months atorvastatin and placebo treatments.**

and hepatic lipoproteins would partly be due to an increase in lipoprotein uptake by receptor-mediated pathways, ie, LDL-receptor.

We have expanded on the study by Parhofer et al[24] in healthy controls by showing a reduction in a more specific marker of intestinal lipoproteins, total postprandial $apoB_{48}$ AUC. Consistent with the notion of improved clearance, Santos et al[34] showed by using a functional assay of chylomicron clearance that pravastatin increased the fractional catabolic rate of chylomicron-like emulsions in normotriglyceridemic men with CAD. In our study, we found no change with treatment in the IAUC for $apoB_{48}$ or triglyceride (ie, corrected for baseline), suggesting that the reduction in plasma chylomicron remnants after atorvastatin therapy was not a consequence of significant modulation of the acute response to ingested fats. Our findings are consistent with those of Twickler et al[35] who investigated the efficacy of simvastatin in familial hypercholesterolemic subjects. In familial hypercholesterolemia subjects, simvastatin significantly reduced the fasting postprandial remnant lipoproteins concentrations, but did not result in an improved postprandial response per se using retinyl palmitate or triglyceride as a marker.

There were significant correlations between the changes in the lathosterol/cholesterol ratio, an indicator of whole body cholesterol synthesis[25] and with both the changes in LDL-cholesterol and $apoB_{100}$ after atorvastatin treatment. As statins inhibit hepatic cholesterol synthesis,[19] the significant association between the reduction in lathosterol/cholesterol ratio with the reduction in $apoB_{100}$ and LDL-cholesterol levels suggests a decrease in hepatic lipoprotein synthesis in the present study. As LDL and chylomicron remnants share a common removal pathway via the liver, reduction in LDL particles would reduce competition for receptor-mediated clearance and may subsequently have led to an increase in chylomicron remnant removal as reflected by the reduction in fasting $apoB_{48}$, RLP-C, and total $apoB_{48}$ AUC levels.

Enhanced clearance via the LDL-receptor and possible reduced competition for receptor-mediated clearance may also have been expected to reduce the $apoB_{48}$ IAUC. Remnant lipoproteins require 4 times as many receptors within close proximity on the plasma membrane for internalisation to occur compared with lipoproteins that utilize $apoB_{100}$ as the binding ligand.[36] It is possible then that increased receptor expression may have chronically modulated chylomicron remnant homeostasis, but have been saturated after an oral lipid challenge of 40 g fat. We would suggest that the differing results of atorvastatin on postprandial lipemia between normolipidemic CAD patients and healthy controls[24] may be due the varying levels of upregulation that will occur between subject groups, which have different levels of baseline LDL-receptor expression.

Using $apoB_{48}$ as a measure of postprandial lipemia, the lowering of fasting $apoB_{48}$ and total AUC levels suggests that atorvastatin acted to lower the total amount of lipid transported in proatherogenic particles in circulation over time. The benefits of this will be a reduction in the number of proatherogenic particles that come in contact with arterial walls and so possibly reduce the risk of atherogenesis. Chylomicron remnants have been shown to be associated with endothelial dysfunction in experimental preparations[37] and a reduction in RLP-C levels with a statin may contribute to the prevention of endothelial dysfunction after a fat load[38] given that coronary endothelial dysfunction may predict the risk for long-term cardiovascular events.[39,40] It may be possible then to hypothesize that the benefits towards reducing the risks of myocardial infarction, stroke, or cardiovascular death found in trials, such as Choles-

terol and Recurring Events (CARE), Long-term Intervention with Pravastatin in Ischemic Disease (LIPID), and Heart Protection Study (HPS)[41-44] involving patients with similar lipid levels, may also be, in part, due to a reduction in postprandial lipemia.

In summary, we have shown that atorvastatin can chronically improve chylomicron homeosatasis in normolipidemic subjects with CAD. Our results and previous clinical trials suggests the possibility that all CAD patients without classical risk factors should be placed on statin therapy, as there may be some benefit in terms of the reduction in cardiovascular risk.

## ACKNOWLEDGMENT

We thank Dr Daniel Talmont for his support, research nurses Enid Pereira and Alison Taylor for clinical help, and Ken Robertson and Richard Scarff for biochemical analyses.

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