Effect of Apheresis of Low-Density Lipoprotein on Peripheral Vascular Disease in Hypercholesterolemic Patients with Coronary Artery Disease

Abraham A. Kroon, MD; Wim N.J.C. van Asten, PhD; and Anton F.H. Stalenhoef, MD

Background: Apheresis of low-density lipoprotein (LDL) is an effective lipid-lowering treatment in hypercholesterolemic patients who have coronary artery disease and are refractory to drugs. More aggressive lipid-lowering therapy may further slow the progression of atherosclerosis.

Objective: To compare the effect of LDL apheresis and simvastatin therapy with the effect of simvastatin therapy alone on the progression of peripheral vascular disease.

Design: Open, randomized, single-center study.

Setting: University hospital.

Patients: 42 men with primary hypercholesterolemia (total cholesterol level > 8.0 mmol/L) and extensive coronary atherosclerosis.

Intervention: Biweekly apheresis of LDL plus simvastatin, 40 mg/d (n = 21), or simvastatin, 40 mg/d (n = 21), for 2 years.

Measurements: Lipid and lipoprotein levels, changes in hemodynamically significant stenoses in the aortotibial tract (measured by ankle:arm systolic blood pressure ratio combined with Doppler spectrum analysis of the femoral artery), and changes in the mean intima-media thickness of three carotid artery segments.

Results: Mean baseline LDL cholesterol levels decreased from 7.8 to 3.0 mmol/L in the apheresis and simvastatin group and from 7.9 to 4.1 mmol/L in the simvastatin-only group; mean lipoprotein(a) levels decreased from 57.0 to 44.5 mg/dL (change, −19%) in the former group and increased from 38.4 to 44.5 mg/dL (change, 15%) in the latter group. In the apheresis group, the number of patients with hemodynamically significant stenoses in the aortotibial tract decreased from 9 to 7; in the simvastatin-only group, the number increased from 6 to 13 (P = 0.002). Mean intima-media thickness decreased by a mean ± SD of 0.05 ± 0.34 mm in the apheresis group and increased by 0.06 ± 0.38 mm in the simvastatin-only group (P < 0.001). According to multiple regression analysis, changes in apolipoprotein B, total cholesterol, and lipoprotein(a) levels accounted for changes in the aortotibial tract (R² = 0.36); changes in lipoprotein(a) and apolipoprotein A1 levels accounted for changes in the intima-media thickness of the carotid artery (R² = 0.49).

Conclusions: Aggressive lipid lowering with simvastatin and LDL apheresis decreased the intima-media thickness of the carotid artery and prevented an increase in the number of hemodynamically significant stenoses in the lower limbs. Therapy with simvastatin alone did not prevent progression of carotid or aortotibial vascular disease.


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Until recently, intensive lipid lowering using 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors has been the most effective way to slow or stop the progression of coronary atherosclerosis and reduce the number of clinical events in men with established coronary artery disease (1–3). Epidemiologic studies have shown parallel, age-related trends of atherosclerotic lesions in the abdominal aorta, carotid artery, and coronary artery (4, 5). Several studies on regulation of plasma lipid levels (6–15) have measured the extent of peripheral vascular disease. Most of these trials have also shown slowed progression of the intima-media thickness of the carotid artery or of the extent of femoral atherosclerosis.

Continuous apheresis of low-density lipoprotein (LDL) using dextran sulfate cellulose columns selectively removes lipoproteins that contain apolipoprotein B from plasma (16). When apheresis is done regularly, levels of LDL cholesterol decrease to levels that cannot be obtained with drug therapy alone (17). Apheresis may, therefore, help prevent progression of atherosclerosis in selected patients with primary hyperlipidemia and established coronary artery or peripheral vascular disease (9, 18–22). Our study, which was part of the LDL-Apheresis Atherosclerosis Regression Study (LAARS) (22), was a 2-year, open, randomized, single-center study of men with primary hypercholesterolemia (total cholesterol level > 8.0 mmol/L) and extensive...
coronary artery disease. Our objective was to determine whether the very aggressive lowering of LDL cholesterol levels with LDL apheresis plus simvastatin, a potent HMG-CoA reductase inhibitor (23), has a better antiatherosclerotic effect than does the lowering of lipid levels to more conventional levels using simvastatin alone. The results of the primary outcome—changes in coronary artery disease as assessed by quantitative analysis of results of sequential coronary angiography and exercise tolerance tests—were recently described elsewhere (22).

Ultrasoundographic techniques are important surrogate variables for clinical end points in quantitative measurements of atherosclerotic manifestations (24). The ankle:arm systolic blood pressure ratio at rest and during hyperemia is a reproducible way to determine the presence of arterial insufficiency in the lower limbs (25). To differentiate between hemodynamically significant stenoses located in the aortoiliac or the femorotibial tract, measurement of this pressure ratio should be combined with measurement of blood flow velocities in the common femoral artery by using Doppler spectrum analyses (26, 27). High-resolution B-mode ultrasonography of the carotid artery is also an effective and accurate way to assess atherosclerotic changes of the arterial wall (28, 29). This technique has been applied in several studies, and the intima–media thickness of the carotid artery has been shown to reflect generalized atherosclerosis, which is indicated by the association of the intima–media thickness with coronary atherosclerosis and lower-extremity atherosclerosis (30–34).

To evaluate the effect of lipid lowering on progression of peripheral vascular disease in hypercholesterolemic patients with severe coronary artery disease, we sequentially assessed hemodynamically significant stenoses in the lower extremities and the intima–media thickness of the carotid artery. We present the results of this assessment and relate them to changes in lipid and lipoprotein levels.

**Methods**

**Patients and Treatment**

The design of LAARS has been described elsewhere (35). Briefly, eligibility criteria included 1) male sex; 2) age between 30 and 67 years; 3) the following lipid levels, measured in persons receiving a standard lipid-lowering diet (American Heart Association step I) but no other lipid-lowering treatment: a) two successively measured serum total cholesterol levels with an average exceeding 8.0 mmol/L or an LDL cholesterol level greater than 5.8 mmol/L and b) two successively measured fasting serum triglyceride levels with an average less than 5.0 mmol/L; and 4) extensive coronary atherosclerosis, as shown by visual assessment of the baseline coronary angiogram. Patients were excluded if they had had a coronary event in the 3 months before study enrollment; if they had impaired hepatic or renal function, hypertension, diabetes mellitus, severe obesity, hyperhomocysteinemia, homozygous familial hypercholesterolemia, and any secondary hyperlipidemia; or if they smoked more than 10 cigarettes per day.

Patients were recruited from the outpatient clinics of the cardiology and internal medicine departments of the University Hospital of Nijmegen. Patients who were eligible at the end of a 2-month run-in period were randomly assigned to receive either biweekly apheresis of LDL plus simvastatin (40 mg/d) or simvastatin (40 mg/d) alone. Randomization was stratified for the serum total cholesterol and lipoprotein(a) levels, age, and the presence or absence of previous coronary artery bypass graft surgery.

Apheresis of LDL was done using an automated system that contained two small dextran sulfate cellulose columns (MA-01 unit, Liposorber, Kanegafuchi Chemical Industry Co., Osaka, Japan); these columns selectively absorb lipoproteins that contain apolipoprotein B and thereby reduce the level of very-low-density lipoprotein (VLDL), LDL, and lipoprotein(a). A volume of 5000 mL was treated per session, and the process took 3 to 4 hours. Patients in the simvastatin-only group visited the outpatient clinics each month. Patients in both treatment groups also received a resin at the highest tolerable dose if serum cholesterol levels exceeded 8.0 mmol/L for 2 consecutive months; we considered it inappropriate to continue single-drug treatment when cholesterol levels were this high. At each visit, a brief physical examination was done and patients were given additional dietary instructions. Adherence to drug therapy was established by counting pills.

**Biochemical Variables**

In the apheresis group, lipid and lipoprotein levels were measured biweekly (before and immediately after each apheresis session); in the simvastatin-only group, these levels were measured monthly. Apolipoprotein A1, apolipoprotein B, and lipoprotein(a) levels were measured bimonthly in both groups. Serum total cholesterol and fasting triglyceride levels were determined by using enzymatic assays (cholesterol: cholesterol oxidase-phenol amionophenazole peroxidase [CHOD-PAP], Boehringer Mannheim, Mannheim, Germany; triglycerides: Serapak, Miles, Italy). High-density lipoprotein (HDL) cholesterol levels were measured by using the polyelectrolyte glycol 6000 precipitation method (36). Lev-
els of LDL cholesterol were calculated by subtracting HDL cholesterol and VLDL cholesterol from total cholesterol. Samples of apolipoprotein A1, apolipoprotein B, and lipoprotein(a) levels were stored at -80 °C; levels were measured at the end of the study. Apolipoprotein A1 and apolipoprotein B levels were quantified in serum by immunonephelometry (37), and lipoprotein(a) levels were measured by using a specific radioimmunoassay [apolipoprotein(a) radioimmunoassay 100, Pharmacia Diagnostics AB, Uppsala, Sweden].

Lipoprotein levels are increased after completion of LDL apheresis used to selectively remove lipoproteins that contain apolipoprotein B. This increase can be explained by first-order kinetics (38). Therefore, time-averaged concentrations (C_{AVG}) or interval mean levels of total cholesterol, LDL cholesterol, apolipoprotein B, and lipoprotein(a) were calculated by applying a formula derived from the area under the rebound curve: $C_{AVG} = C_{MIN} + 0.73(C_{MAX} - C_{MIN})$, where $C_{MAX}$ is the level before treatment and $C_{MIN}$ is the level immediately after apheresis (22). We used only pretreatment levels of serum triglycerides and HDL cholesterol because triglycerides reach pretreatment levels within 1 to 2 days after apheresis and HDL cholesterol is not influenced by LDL apheresis.

**Measurement of the Ankle:Arm Systolic Blood Pressure Ratio and Doppler Spectrum Analyses**

Measuring blood flow velocities in the common femoral artery by using Doppler spectrum analysis has proven to be an accurate, noninvasive, easily performed screening test for assessing functionally and hemodynamically significant stenoses in the aortoiliac tract (26, 27). Staff at the vascular laboratory, who were blinded to treatment assignment, measured blood flow velocity at baseline, at 1 year, and at 2 years. In a single session, blood flow velocities in the common femoral artery and ankle: arm systolic blood pressure ratios in both limbs were recorded at rest and during reactive hyperemia. Analyses done during reactive hyperemia caused by thigh cuff compression have been shown to enhance the sensitivity for detecting abnormalities of the aortoiliac tract (39). Doppler signals were obtained from the common femoral artery by using an 8-MHz bidirectional continuous-wave Doppler apparatus (Angiodine 2, D.M.S., Montpellier, France), with the probe placed just below the inguinal ligament. Maximum-frequency waveforms were calculated from the spectra. As has been described elsewhere (39, 40), several variables that describe the shape of the waveforms were used. The same Doppler probe was used to determine the ankle:arm systolic blood pressure ratio; for this measurement, the systolic radial artery pressure and the highest pressure in either the dorsalis pedis or posterior tibial artery were used. Hemodynamically significant vascular disease was defined as an at-rest ankle:arm systolic blood pressure ratio less than 0.90 or a decrease of the pressure ratio during reactive hyperemia of 0.20 or greater.

For evaluation of the results, patients were categorized according to changes in stenosis. Patients with at least one new hemodynamically significant lesion in the aortoiliac or femorotibial tract of either side were considered to have worsened. Patients in whom the number of lesions decreased and stable patients who showed no difference in the number or location of hemodynamically significant stenoses were considered to have improved. If a patient needed angioplasty or vascular surgery for progressive claudication, he was considered to have worsened, regardless of the outcome of the test.

**Measurements of the Intima–Media Thickness of the Carotid Artery**

High resolution B-mode ultrasonography of the carotid artery was also done once a year. Ultrasonography could not be done at baseline in the first patients that were enrolled because the method was not available at the start of the study. We could therefore evaluate three sequential measurements (including the baseline measurement) in 11 patients in both groups and two measurements in the remaining patients. Longitudinal scans were done from a fixed latero-lateral angle by using a duplex apparatus (ACUSON 128XP, Cardia-Acuson B.V., Mountain View, California) equipped with a 7-MHz L7384 linear array/5.0-MHz Doppler transducer; anatomical landmarks were the dilatation of the common carotid artery and the flow divider in the carotid artery. Great care was taken to obtain a double-line pattern from the near and far walls. The intima–media thickness was defined as the distance in millimeters between the lumen–intima and media–adventitia interfaces. Although the near and far wall are not identical anatomical correlates (41), combined measurements can be used in an intervention study because rates of progression between both wall measurements do not differ (42). Moreover, including the near wall reduces the variability of the measurement. If a plaque was located in the section where the intima–media thickness should be measured, the plaque thickness was included in the intima–media thickness value. The ultrasonographic images of the arterial segments were stored in real-time on a videotape. Follow-up scans from each patient were obtained by the same sonographer. At the end of the study, the intima–media thickness was analyzed off-line at the Interuniversity Cardiology Institute (Utrecht, the Netherlands) by professional readers who were blinded to treatment as-
Statistical Analysis

Analyses were done using the Student t-test and multivariate analysis of variance for normally distributed data and the Mann–Whitney U test for differences in the means of data that were not normally distributed. Differences in proportions were analyzed using the Yates corrected chi-square test, and analyses for trends in proportions were done using the extended Mantel–Haenszel chi-square test. We did stepwise least-squares multivariate regression analysis using a maximal P value in the F test of 0.05 before a variable could be added and a minimal tolerance (collinearity) of 0.01. Analyses were based on the randomly assigned treatment group (intention to treat). A two-sided P value of less than 0.05 was considered significant. Results are expressed as the mean ± SD, and differences between within-group changes are shown with 95% CIs. We used SPSS software (SPSS Inc., Chicago, Illinois) for all analyses.

Table 1. Baseline Characteristics*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Apheresis and Simvastatin-Only Group (n = 21)</th>
<th>Simvastatin-Only Group (n = 21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>50.2 ± 9.6</td>
<td>53.9 ± 8.7</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>81.5 ± 9.7</td>
<td>80.8 ± 8.6</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>26.6 ± 2.0</td>
<td>26.2 ± 2.0</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>129.3 ± 17.3</td>
<td>126.3 ± 18.1</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>78.2 ± 8.9</td>
<td>76.5 ± 9.0</td>
</tr>
<tr>
<td>Current smokers, n (%)</td>
<td>3 (14.3)</td>
<td>4 (19.0)</td>
</tr>
<tr>
<td>Myocardial infarction, n (%)</td>
<td>16 (76.2)</td>
<td>18 (85.7)</td>
</tr>
<tr>
<td>Coronary artery bypass graft surgery, n (%)</td>
<td>10 (47.6)</td>
<td>10 (47.6)</td>
</tr>
<tr>
<td>Percutaneous transluminal coronary angioplasty, n (%)</td>
<td>2 (9.5)</td>
<td>5 (23.8)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>2 (9.5)</td>
<td>5 (23.8)</td>
</tr>
<tr>
<td>Stroke, n (%)</td>
<td>1 (4.8)</td>
<td>3 (14.3)</td>
</tr>
<tr>
<td>Claudication, n (%)</td>
<td>3 (14.3)</td>
<td>5 (23.8)</td>
</tr>
</tbody>
</table>

* Values are the mean ± SD or number (percentage) of patients. Baseline characteristics did not differ significantly between groups.

Results

Baseline Characteristics

Twenty-one men were enrolled in each group; the baseline characteristics of both groups are shown in Table 1. Sixteen patients in each group were heterozygous for familial hypercholesterolemia (76% of the study sample). Risk factors for atherosclerosis were equally distributed. All patients had severe angiographically shown coronary atherosclerosis. Stenosis of 50% or greater was considered significant; according to this criterion, 17 of 21 men in the apheresis group and 19 of 21 men in the simvastatin-only group had three-vessel coronary artery disease. The other patients had two-vessel disease. Four men in the apheresis group and eight men in the simvastatin-only group had a history of stroke or intermittent claudication. Baseline cholesterol levels were high, and most patients had elevated levels of lipoproteins that contained apolipoprotein B according to inclusion criteria (Table 2). Lipoprotein(a) levels showed a skewed distribution: Median baseline levels were 28.8 mg/dL in the apheresis group and 19.8 mg/dL in the simvastatin-only group. The treatment groups were well balanced, and no significant differences were seen between the groups in baseline characteristics or lipid and lipoprotein levels.

Clinical Events and Patient Evaluation

Two patients, one in each group, had progressive intermittent claudication. The patient from the apheresis group had to have angioplasty of the left common iliac artery 5 months after the study began. The same patient had coronary artery bypass graft surgery for unstable angina at 9 months; after this procedure, the patient received simvastatin only. The patient in the simvastatin-only group who had progressive claudication had abdominal aortic graft surgery after 12 months of treatment.

One patient in the apheresis group was lost to follow-up because he died immediately after coronary surgery was done for unstable angina within 3 months after the study began. Thus, the results of 20 patients in the apheresis group and 21 patients in the simvastatin-only group could be evaluated.

Lipid and Lipoprotein Profiles

Three patients in the apheresis group and 4 in the simvastatin-only group received additional resin treatment, 8 to 24 g of cholestyramine per day. Apheresis of LDL reduced mean total cholesterol levels by 62%, reduced mean LDL cholesterol levels by 78%, reduced mean lipoprotein(a) levels by 71%, and reduced mean apolipoprotein B levels by 72%. Levels of HDL cholesterol were not affected by this
procedure. Differences in treatment effects were established by comparing interval mean levels in the apheresis group with mean levels in the simvastatin-only group. During the study, levels of lipoprotein containing apolipoprotein B were significantly lower in the apheresis group than in the simvastatin-only group (Table 2). In both groups, the increase in HDL cholesterol levels and the decrease in serum triglyceride levels were similar during simvastatin treatment (Table 2). The LDL:HDL cholesterol ratio was reduced from 8.4 to 2.7 (a change of $-67\% \pm 7\%$) in the apheresis group and from 8.5 to 3.9 (a change of $-53\% \pm 7\%$) in the simvastatin-only group (difference between groups, 14.5% [95% CI, 9.9% to 19.1%]). The interval mean lipoprotein(a) level was reduced by 19% to 44.5 ± 54.3 mg/dL in the apheresis group; this reduction was statistically significant (P < 0.001). The total number of patients with hemodynamically significant lesions decreased from 9 to 7; this statistically insignificant change caused significant differences in trends between both groups at the end of the study (P = 0.002; Figure 1). The number of patients who had abnormalities of the aortoiliac tract decreased from 4 to 1 (P = 0.003), and the number of patients with femorotibial stenoses decreased from 8 to 6 (P < 0.001). Eighteen of 20 patients (90%) in the apheresis group and 8 of 21 patients in the simvastatin-only group showed a reduction or no change in the number of hemodynamically significant stenoses in the whole aortoiliac tract (P = 0.002) (relative risk, 2.4 [CI, 1.3 to 4.2]).

When we categorized patients into those who showed an increase and those who showed no change or a reduction in the number of hemodynamically significant stenoses, the decreases in levels of total cholesterol, LDL cholesterol, lipoprotein(a), attributable to an increase in the number of femorotibial lesions (from 4 to 11). The number of patients with abnormalities of the aortoiliac tract increased from 5 to 7. In the apheresis group, the total number of patients with hemodynamically significant lesions decreased from 9 to 7; this statistically insignificant change caused significant differences in trends between both groups at the end of the study (P = 0.002; Figure 1). The number of patients who had abnormalities of the aortoiliac tract decreased from 4 to 1 (P = 0.003), and the number of patients with femorotibial stenoses decreased from 8 to 6 (P < 0.001). Eighteen of 20 patients (90%) in the apheresis group and 8 of 21 patients in the simvastatin-only group showed a reduction or no change in the number of hemodynamically significant stenoses in the whole aortoiliac tract (P = 0.002) (relative risk, 2.4 [CI, 1.3 to 4.2]).

When we categorized patients into those who showed an increase and those who showed no change or a reduction in the number of hemodynamically significant stenoses, the decreases in levels of total cholesterol, LDL cholesterol, lipoprotein(a),

### Table 2. Changes in Lipid and Lipoprotein Levels*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Apheresis and Simvastatin Group (n = 21)</th>
<th>Simvastatin-Only Group (n = 21)</th>
<th>Difference between Within-Group Changes (95% CI)</th>
<th>P Value for Difference between Treatment Groups*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline Value</td>
<td>Percentage Change</td>
<td>Baseline Value</td>
<td>Percentage Change</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>9.72 ± 1.84</td>
<td>−52.9% ± 6.6%</td>
<td>9.85 ± 2.17</td>
<td>−39.5% ± 7.7%</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>2.32 ± 1.03</td>
<td>−17.4% ± 24.4%</td>
<td>2.64 ± 1.33</td>
<td>−26.5% ± 20.3%</td>
</tr>
<tr>
<td>Low-density lipoprotein</td>
<td>7.78 ± 1.86</td>
<td>−62.9% ± 8.3%</td>
<td>7.85 ± 2.34</td>
<td>−47.4% ± 8.1%</td>
</tr>
<tr>
<td>cholesterol, mmol/L</td>
<td>0.99 ± 0.18</td>
<td>17.7% ± 13.6%</td>
<td>0.92 ± 0.19</td>
<td>13.7% ± 10.9%</td>
</tr>
<tr>
<td>Lipoprotein(a), mg/dL</td>
<td>57.0 ± 63.9</td>
<td>−18.6% ± 18.0%</td>
<td>38.4 ± 39.7</td>
<td>14.9% ± 16.3%</td>
</tr>
<tr>
<td>Apolipoprotein B, g/L</td>
<td>2.59 ± 0.47</td>
<td>−49.0% ± 7.6%</td>
<td>2.60 ± 0.61</td>
<td>−31.0% ± 17.0%</td>
</tr>
<tr>
<td>Apolipoprotein A1, g/L</td>
<td>1.43 ± 0.29</td>
<td>−5.3% ± 13.0%</td>
<td>1.46 ± 0.38</td>
<td>−5.4% ± 16.8%</td>
</tr>
</tbody>
</table>

* Values are the mean ± SD. To convert total cholesterol values to mg/dL, multiply by 38.67; to convert triglyceride values to mg/dL, multiply by 88.57.
† Mann–Whitney U test or t-test.
Table 3. Change in Lipid and Lipoprotein Levels in Patients Showing an Increase in the Number of Hemodynamically Significant Stenoses in the Aortoiliac and Femorotibial Tract Compared with Patients Showing No Change or a Reduction in the Number of Stenoses*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients with Worsened Stenosis (n = 15)</th>
<th>Patients with No Change or Improvement in Stenosis (n = 26)</th>
<th>Difference between Within-Group Changes (95% CI)</th>
<th>P Value for Difference between Groups†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline Value</td>
<td>Percentage Change</td>
<td>Baseline Value</td>
<td>Percentage Change</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>9.75 ± 2.19</td>
<td>-37.8% ± 7.7%</td>
<td>9.88 ± 1.92</td>
<td>-49.2% ± 7.8%</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>2.75 ± 1.24</td>
<td>-25.7% ± 14.4%</td>
<td>2.49 ± 1.27</td>
<td>-25.3% ± 16.1%</td>
</tr>
<tr>
<td>Low-density lipoprotein cholesterol</td>
<td>7.70 ± 2.34</td>
<td>-46.6% ± 7.2%</td>
<td>7.91 ± 2.07</td>
<td>-58.3% ± 9.3%</td>
</tr>
<tr>
<td>High-density lipoprotein cholesterol</td>
<td>0.93 ± 0.19</td>
<td>11.0% ± 9.2%</td>
<td>0.95 ± 0.19</td>
<td>15.9% ± 12.6%</td>
</tr>
<tr>
<td>Lipoprotein(a), mg/dL</td>
<td>44.0 ± 40.9</td>
<td>12.0% ± 16.2%</td>
<td>47.3 ± 60.5</td>
<td>-12.8% ± 16.3%</td>
</tr>
<tr>
<td>Apolipoprotein B, g/L</td>
<td>2.65 ± 0.58</td>
<td>-32.9% ± 14.8%</td>
<td>2.56 ± 0.54</td>
<td>-44.7% ± 12.1%</td>
</tr>
<tr>
<td>Apolipoprotein A1, g/L</td>
<td>1.50 ± 0.38</td>
<td>-2.8% ± 13.7%</td>
<td>1.43 ± 0.31</td>
<td>-1.0% ± 14.7%</td>
</tr>
</tbody>
</table>

* No differences in baseline levels were seen between groups. Values are the mean ± SD. To convert total cholesterol values to mg/dL, multiply by 38.67; to convert triglyceride values to mg/dL, multiply by 88.57.
† Mann-Whitney U test or t-test.

and apolipoprotein B were significantly greater in the group that had no change or a reduction (Table 3). Indeed, significant correlations were found between the worsening or improvement of lesions in the aortotibial tract and absolute changes from baseline in levels of total cholesterol ($r = 0.46$), LDL cholesterol ($r = 0.38$), apolipoprotein B ($r = 0.30$), and lipoprotein(a) ($r = 0.44$). This correlation indicates that more aggressive lipid lowering was associated with a reduction in the number of hemodynamically significant stenoses. Multiple regression analyses showed that the following variables accounted for changes in the aortotibial tract: mean apolipoprotein B level during the study ($b = 0.19$ [CI, 0.10 to 0.22]; $P = 0.005$), absolute change from baseline in total cholesterol levels ($b = 0.20$ [CI, 0.12 to 0.28]; $P = 0.005$), and absolute change from baseline in lipoprotein(a) levels ($b = 0.16$ [CI, 0.07 to 0.24]; $P = 0.01$). Stepwise addition of other variables did not further significantly improve the variance (total $R^2 = 0.36; P = 0.001$).

Intima–Media Thickness of the Carotid Artery

Baseline concentrations of lipids and lipoproteins of the group of 22 men in whom intima–media thickness was measured three times, including at baseline, did not differ from those in the entire study group (data not shown). At baseline, the intima–media thicknesses of the bifurcation and the internal carotid artery were significantly different between groups (Table 4). During the study, however, the mean intima–media thickness of all carotid segments gradually and significantly decreased in the apheresis group; in contrast, the thickness in the simvastatin-only group increased. Categorization of patients into those who had reduction or no change in mean intima–media thickness ($n = 11$) and those who had increased thickening ($n = 11$) again showed that reductions in levels of total cholesterol, LDL cholesterol, lipoprotein(a), and apolipoprotein B were significantly greater in the former group (data similar to those shown in Table 3) and that changes in HDL cholesterol, serum triglyceride, and apolipoprotein A1 levels did not differ (data not shown). According to multiple regression analysis, change in mean intima–media thickness was explained by absolute changes in apolipoprotein A1 levels ($b = 0.13$ [CI, 0.07 to 0.31]; $P = 0.02$) and lipoprotein(a) levels ($b = 0.43$ [CI, 0.23 to 0.63]; $P = 0.004$). No other variables further significantly improved total variance ($R^2 = 0.49; P = 0.002$).

A positive correlation was found between the

Table 4. Change in Mean Intima–Media Thickness in Carotid Artery Segments

<table>
<thead>
<tr>
<th>Location</th>
<th>Apheresis and Simvastatin Group (n = 11)</th>
<th>Simvastatin-Only Group (n = 11)</th>
<th>Difference between Within-Group Changes (95% CI)</th>
<th>P Value for Difference between Groups†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline Intima–Media Thickness</td>
<td>Change</td>
<td>Baseline Intima–Media Thickness</td>
<td>Change</td>
</tr>
<tr>
<td>Bifurcation</td>
<td>1.11 ± 0.54</td>
<td>-0.13 ± 0.47</td>
<td>0.92 ± 0.29</td>
<td>0.16 ± 0.46</td>
</tr>
<tr>
<td>Common carotid artery</td>
<td>0.81 ± 0.18</td>
<td>-0.05 ± 0.12</td>
<td>0.80 ± 0.22</td>
<td>-0.03 ± 0.27</td>
</tr>
<tr>
<td>Internal carotid artery</td>
<td>0.83 ± 0.27</td>
<td>-0.04 ± 0.30</td>
<td>0.91 ± 0.37</td>
<td>0.03 ± 0.39</td>
</tr>
<tr>
<td>All carotid artery segments</td>
<td>0.91 ± 0.38</td>
<td>-0.05 ± 0.34</td>
<td>0.88 ± 0.30</td>
<td>0.06 ± 0.38</td>
</tr>
</tbody>
</table>

* Values are the mean ± SD and were obtained in a subgroup of 22 patients.
† Multivariate analysis of variance.
reduction in mean intima–media thickness of the carotid artery and the reduction of hemodynamically significant stenoses in the aortoiliac tract, expressed as categorical changes (worsened, stable, or improved) \( (b = 0.13 \ [CI, 0.07 \text{ to } 0.31]; P = 0.048) \) or as a change in a score that describes the shape of the Doppler spectrum waveforms \( (b = 0.21 \ [CI, 0.15 \text{ to } 0.28]; P = 0.009) \) (Figure 2) (39).

**Discussion**

The LDL-Apheresis Atherosclerosis Regression Study (22) evaluated whether very aggressive lipid lowering in men with extensive coronary artery disease more effectively slows the progression of atherosclerosis; changes in the extent of coronary artery disease were primary outcome measures. Our study focused on secondary outcome measures. We showed that LDL apheresis plus simvastatin treatment prevented an increased prevalence of hemodynamically significant stenosis in the aortoiliac tract and reduced the mean intima–media thickness of the carotid artery. Two years of very aggressive lipid-lowering treatment (apheresis plus simvastatin) reduced the size of early peripheral atherosclerotic lesions and arrested progression of advanced lesions; conventional treatment did not prevent progression of early or advanced peripheral lesions.

Several studies (6–10) have shown the effect of lipid lowering on femoral atherosclerosis. Only one uncontrolled study (9) showed the beneficial effect of LDL apheresis in patients with arteriosclerotic obliteration. Both the Program on the Surgical Control of Hyperlipidemias (POSCH) (7) and the Cholesterol Lowering Atherosclerosis Study (CLAS) (8) showed that long-term lipid-lowering therapy reduced the extent of angiographically determined femoral atherosclerosis in patients with established coronary heart disease. These findings agreed with ours. However, in the population-based Kuopio Atherosclerosis Prevention Study (KAPS) (10), pravastatin treatment decreased LDL cholesterol levels from 4.9 mmol/L to 3.5 mmol/L but did not reduce the annual rate of progression of the intima–media thickness of the femoral arteries. Some studies (10–14) have also shown a decrease in or reduced progression of the carotid artery intima–media thickness during lipid-lowering therapy. After 2 years of treatment, the CLAS investigators (11) showed that the mean intima–media thickness of the common carotid artery was reduced by \( 0.05 \pm 0.06 \text{ mm} \); the Monitored Atherosclerosis Regression Study (MARS) (12) showed a decrease of \( 0.06 \pm 0.11 \text{ mm} \) at 2 years. These decreases are similar to the decrease seen in our apheresis group.

The findings in our simvastatin-only group are remarkable; these patients do not seem to have benefited from cholesterol-lowering drug therapy. However, the placebo groups in CLAS, MARS, and the Pravastatin to Limit Atherosclerosis in the Coronary arteries (PLAC-II) study (14)—all of which enrolled persons with coronary artery disease and had a mean in-trial LDL cholesterol level similar to that in our simvastatin-only group—showed progression of carotid intima–media thickness. Moreover, patients in KAPS (10) who received pravastatin (LDL cholesterol level, 3.5 mmol/L) still showed progression of carotid intima–media thickness; in the Asymptomatic Carotid Artery Progression Study (ACAPS) (13), intima–media thickness decreased in patients to whom lovastatin was given to decrease LDL cholesterol levels to 2.9 mmol/L. Thus, although there are important differences among these studies and although we analyzed only a small group of patients, our data seem to highlight the fact that very aggressive therapy to decrease LDL cholesterol levels is necessary to reduce the progression of atherosclerosis in both peripheral vascular beds.

Our results confirm the usefulness of extracorporeal therapy in achieving and maintaining low LDL cholesterol levels and support the findings of the first randomized study of apheresis (20). The reduction of baseline LDL cholesterol levels by 63% is similar to the decrease seen in other studies that used lipid-lowering drugs plus apheresis (19, 43). On the other hand, the 47% reduction in LDL cholesterol levels seen in our simvastatin-only group may be considered a good response to treatment (23). This reduction is probably the result of frequent monitoring of the patients.

The effect of risk factors on the development of atherosclerosis differs among the arterial segments. Cigarette smoking, hypertension, and age have been shown to be more powerful predictors of the presence of peripheral vascular disease than are lipids
and lipoproteins (44, 45). In LAARS, only the effects of changes in lipid and lipoprotein levels could be analyzed. The observed correlations with total levels of cholesterol, apolipoprotein B, apolipoprotein A1, and lipoprotein(a) agree with data from population-based and intervention studies (46–48). The influence of lipoprotein(a) as a risk factor should be discussed in more detail because LDL cholesterol apheresis is one of the few treatments that can reduce the concentration of this substance (49). The reduction of lipoprotein(a) levels in our apheresis group may be somewhat limited: The increase in lipoprotein(a) levels related to simvastatin treatment was also seen in the simvastatin-only group. This result has also been seen in other reports (22, 50). Still, significantly different trends in lipoprotein(a) levels were seen in both groups, and multiple regression analysis indicated an important relation with change in lipoprotein(a) levels. However, decreasing LDL levels may be as important for the outcome because mean lipoprotein(a) levels during the study were the same in both treatment groups. The Familial Hypercholesterolaemia Regression Study (20) recently showed that further reduction of lipoprotein(a) levels by LDL cholesterol apheresis did not further slow the progression of coronary artery disease compared with drug treatment, which decreased LDL cholesterol levels to the same extent. This finding indicates that the lipoprotein(a) level is less important when combined with low LDL cholesterol levels. However, the Familial Hypercholesterolaemia Regression Study did not include patients with elevated lipoprotein(a) levels. Thus, in our patients, who had elevated LDL cholesterol levels, decreases in lipoprotein(a) levels may account for part of the effect on peripheral vascular disease.

It is plausible to criticize the results from Doppler spectrum analyses and ankle:arm systolic blood pressure ratio measurements if one presumes that rheologic changes induced by LDL apheresis influenced the results. Indeed, early improvements in the clinical symptoms of claudication and pectoral angina are assumed to be initially induced by correction of rheologic properties of blood (9, 51). Reductions by dextran-sulfate adsorption of fibrinogen, factor VIII, and other coagulation factors have been reported to last no longer than 1 to 2 days (52). Still, viscosity of whole blood and plasma has been shown to be reduced for as long as 1 week (53). Thus, we cannot exclude the possibility that improved rheology influenced the measurements of hemodynamic stenosis after 1 year of treatment (while apheresis was still being done). At study end, however, the assessments were done 3 to 4 weeks after the last treatment; rheologic changes had disappeared by that time.

The safety and efficacy of LDL apheresis in LAARS have been reported elsewhere (22). In general, adverse events are infrequent and similar to those seen with any extracorporeal treatment. The most frequently reported adverse effects are hypotension and chills; frequencies of these conditions range from 0.2% to 1.1% and 0.3% to 6.0%, respectively (17, 22, 51). The efficacy of the treatment depends on the lipid levels before and after treatment and on the return of lipids to plasma after treatment (38, 54). The combination of LDL apheresis and simvastatin therapy can be expected to reduce the rate of the rebound in serum cholesterol after apheresis; this effect permits prolongation of the intervals between apheresis sessions (54). Nevertheless, LDL apheresis done every 2 weeks entails a major commitment for the patient and, given the high cost of this treatment, for the medical community. Therefore, LDL apheresis should be reserved for the few patients who meet the criteria for the accepted indications: homozygous familial hypercholesterolemia, coronary artery disease, and resistance to drug treatment (17).

In conclusion, our results confirm that hypercholesterolemic patients with established coronary artery disease or peripheral vascular disease should be treated with a combination of lipid-lowering therapy until LDL cholesterol levels are decreased to less than 3.0 mmol/L. The combination of LDL apheresis and cholesterol-lowering drugs in patients with a high risk for cardiovascular events is feasible and has been shown to reduce the extent of peripheral vascular disease. However, LDL apheresis should be considered only in patients who have hypercholesterolemia and are refractory to combined drug treatment.

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AD LIBITUM

Medical Marriage

Since she had always dreamt
of making love on a beach
and he was dreaming of furrowed fields
they figured it was time

And as soon as the youngest fell off
to his nest below their bed
and the events of the day had
drifted to the corners of the room
they took the deeply planted
signs to be what they meant to be
and embraced

Later, after two more phone calls
they marvelled at their jerry-built lives
at the Rubegoldbergian blueprint
they swore once again to revise
and sang the praises of soundly sleeping children
answering machines and other small gifts
only God could have devised

Martin Kohn, PhD
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