LDL-Apheresis Atherosclerosis Regression Study (LAARS)
Effect of Aggressive Versus Conventional Lipid Lowering Treatment on Coronary Atherosclerosis

Abraham A. Kroon, MD; Wim R.M. Aengevaeren, MD; Tjeerd van der Werf, MD; Gerard J.H. Uijen, PhD; Johan H.C. Reiber, PhD; Albert V.G. Bruschke, MD; Anton F.H. Stalenhoef, MD

Background Intensive lipid lowering may retard the progression of coronary atherosclerosis. LDL-apheresis has the potential to decrease LDL cholesterol to very low levels. To assess the effect of more aggressive lipid lowering with LDL-apheresis, we set up a randomized study in men with hypercholesterolemia and severe coronary atherosclerosis.

Methods and Results For 2 years, 42 men were treated with either biweekly LDL-apheresis plus medication or medication alone. In both groups a dose of simvastatin of 40 mg per day was administered. Baseline (mean±SD) LDL cholesterol was 7.6±1.9 mmol·L⁻¹ and 7.9±2.3 mmol·L⁻¹ in the apheresis and medication groups, respectively. The mean reduction in LDL cholesterol was 63% (to 3.0 mmol·L⁻¹) and 47% (to 4.1 mmol·L⁻¹), respectively. Primary quantitative coronary angiographic end points were changes in average mean segment diameter and minimal obstruction diameter. No differences between the apheresis and medication groups were found in mean segment diameter (−0.01±0.16 mm versus 0.03±0.16 mm, respectively).

The relation between total cholesterol and LDL cholesterol levels and the incidence of CAD is well established.¹² Primary and secondary prevention trials, predominantly conducted in men with hypercholesterolemia, have shown that lipid lowering regimens result in less progression of angiographic lesions.³ Regression of coronary atherosclerosis is demonstrated to a limited extent in some patients in most of these trials.⁴⁻¹² The common denominator of these trials is reduction of LDL cholesterol.¹³ Until recently, intensive lipid lowering in men with established CAD using HMG-CoA reductase inhibitors was the most effective means in terms of slowing or arrest of progression of coronary atherosclerosis¹⁴,¹⁵ and consequently reducing the number of clinical events.¹⁶

Continuous LDL-apheresis, using dextran sulfate cellulose columns, selectively removes apolipoprotein B-containing lipoproteins from plasma.¹⁷,¹⁸ The performance of regular apheresis permits the achievement of lower levels of LDL cholesterol, which is not usually possible to attain with drug therapy alone. The application of this method may offer opportunities in the prevention of progression or even inducing regression of coronary atherosclerosis in selected patients with primary hyperlipidemia and established CAD.¹⁹⁻²²

The quantitative computerized analysis of the extent of atherosclerosis on QCA has been developed and extensively evaluated for angiographic trials.²³⁻²⁵ Despite certain limitations, QCA is one of the most precise procedures available for assessing progression or regression of CAD.²⁶ Given the relatively small changes in the severity of lesions demonstrated in angiographic trials and the unclear clinical benefits of such changes, the addition of measurements to predict the functional significance of changes in coronary stenosis seems important.²⁷

The LDL-Apheresis Atherosclerosis Regression Study (LAARS) was designed as a prospective, open, randomized, single-center study in men with primary hypercholesterolemia and extensive CAD. The objective was to determine whether more aggressive LDL cholesterol lowering, with biweekly LDL-apheresis plus the HMG-CoA reductase inhibitor simvastatin, more effectively exerts an antiatherosclerotic effect than lipid lowering to more conventional cholesterol levels with simvastatin alone. In this article, the results of sequential exercise tolerance tests and

© 1996 American Heart Association, Inc.
quantitative computer-assisted analysis of coronary angiograms during 2 years of treatment are described and related to the lipid and lipoprotein levels. The results of functional measurements of coronary blood flow by means of videodensitometry will be presented separately.

Methods

Subjects and Treatment

From January 1990 until May 1992, men aged between 30 and 67 years who underwent diagnostic coronary angiography for angina pectoris were screened for eligibility. Included were patients with a mean of two successive serum total cholesterol determinations >8.0 mmol \( \text{L}^{-1} \) or LDL cholesterol >5.8 mmol \( \text{L}^{-1} \) and a mean of two successive fasting serum triglyceride measurements <5.0 mmol \( \text{L}^{-1} \) on a standard lipid lowering diet without other lipid lowering treatments and expected to slow down the postapheresis rebound in serum lipids and lipoproteins and some extra laboratory safety parameters (hemogram, calcium, and total protein level) were measured before and immediately after each LDL-apheresis. Serum total cholesterol and fasting triglycerides were determined enzymatically (CHOD-PAP, No. 237574, Boehringer Mannheim GmbH, and Sera-PAK, No. 6639, Miles). HDL cholesterol was determined with the polyethylene glycol 6000 precipitation method.\(^{32}\) LDL cholesterol was calculated by subtraction. Samples for apo Al, apo B, and Lp(a) were measured bimonthly. In the apheresis group, lipids and lipoproteins and some extra laboratory safety parameters (hemogram, calcium, and total protein level) were measured before and immediately after each LDL-apheresis. Serum total cholesterol and fasting triglycerides were determined enzymatically (CHOD-PAP, No. 237574, Boehringer Mannheim GmbH, and Sera-PAK, No. 6639, Miles). HDL cholesterol was determined with the polyethylene glycol 6000 precipitation method.\(^{32}\) LDL cholesterol was calculated by subtraction. Samples for apo Al, apo B, and Lp(a) were measured at −80°C and determined at the end of the study. Apo AI and apo B were quantified in serum by immunonephelometry.\(^{33}\) Lp(a) was measured by a specific radioimmunoassay (apo[a] RIA 100, Pharmacia Diagnostics AB). Hyperhomocysteinemia was excluded by measuring fasting homocysteine levels.\(^{34}\) Fibrinogen levels did not differ between both groups. Apheresis produced an acute 35% reduction of fibrinogen, returning to pretreatment levels between 2 and 7 days (n=11, data not shown).

The selective removal of apo B-containing lipoproteins with LDL-apheresis causes sawtoothlike alterations in lipoprotein concentrations.\(^{35}\) The increase of lipoprotein levels after the treatment can be explained by first-order kinetics.\(^{36-38}\) Therefore, time-averaged concentrations \( (C_{AVG}) \) or interval means of total cholesterol, LDL cholesterol, apo A1, and Lp(a) were calculated by applying a formula derived from the rebound curves that were constructed for each patient at one occasion:

### Table 1. Baseline Characteristics

| Age, y | 50.2±9.6 | 53.9±8.7 | 0.43 |
| Weight, kg | 81.5±9.7 | 80.8±8.6 | 0.88 |
| Body mass index, kg m\(^{-2} \) | 26.6±2.0 | 26.2±2.0 | 0.94 |
| Blood pressure, mm Hg | | | |
| Systolic | 129.3±17.3 | 126.3±18.1 | 0.56 |
| Diastolic | 78.2±8.9 | 78.5±8.0 | 0.83 |
| Current smoking | 3 (14.3) | 4 (19.0) | 1.00 |
| Vascular disease | | | |
| Infarction | 16 (76.2) | 18 (85.7) | 0.69 |
| CAGB | 10 (47.6) | 10 (47.6) | 0.75 |
| PTCA | 2 (9.5) | 5 (23.8) | 0.41 |
| Hypertension | 2 (9.5) | 5 (23.8) | 0.41 |
| Stroke | 1 (4.8) | 3 (14.3) | 0.80 |
| Claudication | 3 (14.3) | 5 (23.8) | 0.69 |
| Drug treatment | | | |
| β-Blocker | 10 (47.6) | 14 (66.7) | 0.35 |
| Ca channel blockers | 4 (19.0) | 7 (33.3) | 0.48 |
| Long-acting nitrates | 4 (19.0) | 4 (19.0) | 0.99 |
| Anticoagulants | 3 (14.3) | 6 (28.6) | 0.45 |
| Platelet aggregation inhibitors | 4 (19.0) | 8 (38.1) | 0.31 |

Values indicate numbers (percentages) or mean±SD. *t tests or χ\(^2\) tests where appropriate.
\[ C_{AVG} = C_{MIN} + 0.73(C_{MAX} - C_{MIN}) \]

where \( C_{MAX} \) is the pretreatment level and \( C_{MIN} \) the levels immediately after apheresis.\(^9\) For serum triglycerides and HDL cholesterol, only pretreatment levels were used in the analysis because triglycerides reach pretreatment levels within 1 to 2 days after apheresis and HDL cholesterol is not influenced by LDL-apheresis.

**Exercise Tests**

Bicycle exercise tests were performed at baseline and 12 and 24 months after the start of the study. The assessments at the end of the study were done 3 to 4 weeks after the last apheresis. An electronic braked ergometer (Marquette Case 15, Marquette Electronics Inc) was used, starting at a load of 50 W and raising it every minute by 10 W during continuous ECG monitoring to maximum exercise limited by chest discomfort or usual criteria for stopping the test. Blood pressure and 12-lead ECG registration were monitored at rest, at maximum exercise, and every minute during the test. Automated calculation of ST-segment depression was performed at a point located 80 ms beyond the J-point. Data were corrected for the systolic blood pressure–heart rate product at maximal load. An additional exercise thallium scintigram was performed when the bicycle exercise test was not conclusive due to a maximum heart frequency ≤85% of the predicted value corrected for age and body mass and/or the predicted load ≤80% without ST-segment changes.

**Coronary Angiography**

The coronary angiograms were obtained at baseline and after 2 years of treatment, 4 weeks after the last apheresis, using the same protocol as that described for the Regression Growth Evaluation Statin Study (REGRESS).\(^12\) During both procedures, the same nonionic iso-osmolar contrast agent (Iohexol 350, Nycomed AS) and the same cineangiographic techniques were used, according to standard requirements for quantitative analysis.\(^25\) A centimeter grid was filtered to adjust for pincushion distortion. The same type and diameter of catheters were used in both procedures and were used as a scaling device in QCA analysis. The protocol required administration of 5 to 10 mg of isosorbide dinitrate sublingually 5 minutes before the first intracoronary injection of contrast, which was repeated during the procedure if necessary. Twelve to 15 coronary segments were filmed in two projections.\(^46\) Preferably, end-diastolic frames were selected for blinded computer-assisted quantitative analysis of paired angiograms, which was performed at the Heart Core Angiographic Reference Laboratory at the University Hospital of Leiden using the Cardiovascular Measurement System (CMS Medis Medical Imaging Systems, CMS version 2.3D).\(^41\) This system uses a high-quality cinevideo converter (CAP 35E) that allows a selected cineframe to be projected onto a digital camera through a zoom lens (magnification ×2.3). The video signal of the magnified region was digitized at a matrix size of 512×512×8 bits. For calibration, the boundaries of a nontapering part of the catheter were determined automatically over a length of approximately 2 cm. To assess the contours of the vessel, the beginning and the end of the specific coronary segment had to be indicated, after which a path line was computed connecting these two points. The contours of the vessel were then computed in multiple iterations by the minimal cost contour detection technique. The edge strength of a point was based on the weighted sum of the first and second derivative functions; this edge strength was corrected for the limited resolution of the entire imaging chain, a procedure that is particularly important for the accurate measurement of small vessels. A diameter function was determined in absolute terms (in millimeters) by computing the shortest distances between the left and right contours along the vessel centerline. The reference diameter was defined as previously described.\(^42\) Primarily, MOD, as a measure for localized atherosclerosis, and the MSD, as a measure for diffuse changes, were assessed. Only segments without overlap and minimal foreshortening were analyzed, including bypass segments. PTCA segments from procedures after the randomization and segments distal to an occlusion were excluded from analysis. Patients were categorized with regard to MOD and clinical events as regressors, stable patients, and progressors, according to the REGRESS protocol.\(^12\) Patients with at least one lesion worsening by ≥0.4 mm or development of a lesion that reduced the lumen diameter by ≥0.4 mm were defined as progressors. Regressors were patients with at least one lesion improving ≥0.4 mm and no lesions worsening ≥0.4 mm. Stable patients had no lesions worsening or improving by ≥0.4 mm. Patients with regressing and progressing lesions were considered to be progressors because simultaneous progression and regression reflect an unstable process in coronary atherosclerosis.\(^10\) If a patient previously had a myocardial infarction or unstable angina, he was considered to be a progressor irrespective of angiographic outcome. Additionally, the percentage of stenoses in each segment was calculated as the mean of the percent stenosis in two projections, ensuring comparability of the segments by available angiographic landmarks, in the baseline and follow-up angiograms. Only segments with a mean percentage of stenosis ≥20% at either baseline or follow-up were analyzed. If only one projection was available of a stenosis ≥20%, this figure was used as the mean percent stenosis in that particular angiogram. New lesions were defined as <20% at baseline and ≥20% at follow-up.

**Statistical Analysis**

The sample size was limited for logistic reasons to approximately 40 patients. At the start of the study, the observed standard deviation for mean progression in coronary segments from previous trials was 0.23 to 0.32 mm (0.32 mm with baseline total cholesterol >6.00 mmol · L\(^{-1}\)). Considering the expected changes in cholesterol levels, a minimal sample size of 19 patients in each group was calculated (SD=0.25 mm, expected difference=0.20 mm).\(^22\) Analyses were performed with procedures available in the Statistical Package for Social Sciences (SPSS Inc) with use of the Student’s t test and multivariate ANOVA (with correction for repeated measures or covariates) for normally distributed data or the Mann-Whitney U test for differences in means of not normally distributed data. Differences in proportions were analyzed with the (Yates’) corrected \(x^2\) test, and analyses for trends in proportions were performed with the extended Mantel-Haenszel \(x^2\) test. A two-sided Fisher’s exact test was used when the total number of cases was less than 15. For measures of agreement, the Pearson product-moment correlation coefficient was used. Analyses were based on randomization assignment, except for one patient in the apheresis group, who died within 3 months from the start of the study. A two-sided probability value of <0.05 was considered significant. Results are expressed as mean±SD unless otherwise indicated.

**Results**

**Baseline Characteristics**

In both treatment groups, 21 men were enrolled for whom baseline characteristics are shown in Table 1. In both groups, 16 patients were heterozygous for familial hypercholesterolemia (76% of the study population). Risk factors for atherosclerosis were equally distributed. All patients had severe coronary atherosclerosis. A previous history of myocardial infarction was present in 16 versus 18 men in the apheresis and medication groups, respectively, and CABG had been performed in 10 men in both groups. By the criterion of a stenosis of ≥50% being considered significant, 17 of 21 men in the
Table 2. Changes in Lipids and Lipoproteins: Baseline and Treatment Levels

<table>
<thead>
<tr>
<th></th>
<th>Apheresis (n=21)</th>
<th>Medication Only (n=21)</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Basal</td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>Total cholesterol, mmol·L⁻¹</td>
<td>9.72±1.64</td>
<td>5.60±1.26</td>
<td>2.06±0.46</td>
</tr>
<tr>
<td>Triglycerides, mmol·L⁻¹</td>
<td>2.32±1.03</td>
<td>1.83±0.76</td>
<td>0.48±0.28</td>
</tr>
<tr>
<td>LDL cholesterol, mmol·L⁻¹</td>
<td>7.78±1.86</td>
<td>3.72±1.26</td>
<td>0.82±0.41</td>
</tr>
<tr>
<td>HDL cholesterol, mmol·L⁻¹</td>
<td>0.93±0.16</td>
<td>1.09±0.20</td>
<td>1.09±0.20</td>
</tr>
<tr>
<td>Apolipoprotein(a), mg·dl⁻¹</td>
<td>57.0±63.9</td>
<td>59.1±68.8</td>
<td>13.8±15.3</td>
</tr>
<tr>
<td>Apolipoprotein A1, g·L⁻¹</td>
<td>1.43±0.29</td>
<td>1.34±0.17</td>
<td>1.08±0.13</td>
</tr>
<tr>
<td>Apolipoprotein B, g·L⁻¹</td>
<td>2.59±0.47</td>
<td>1.65±0.43</td>
<td>0.45±0.16</td>
</tr>
</tbody>
</table>

Data are mean±SD. Apheresis group: 52 measurements per patient. Medication group: 26 measurements per patient. Before indicates pretreatment levels (C₀; after, posttreatment levels (Cₚ); interval mean, time-averaged levels (Cᵥ); calculated as follows: Cᵥ=Cₚ+0.73(Cₚ−C₀) (see text); % change, difference between basal and mean levels; P, probability values of differences between interval mean in the apheresis group and mean levels in the medication group (t test or Mann-Whitney U test where appropriate). To convert values for total cholesterol to mg/dL, multiply by 3.867; to convert values for triglycerides to mg/dL, multiply by 88.57.

apheresis group and 19 of 21 men in the medication group had three-vessel disease of the coronary arteries, and the other patients had two-vessel disease. Drug treatment at randomization showed a higher but not statistically significant number of patients in the medication group using anticoagulants or platelet aggregation inhibitors (Table 1). At the time the study started, anticoagulants or platelet inhibitors were used less. Baseline cholesterol levels were high, and predominant elevation of apo B-containing lipoproteins was found in agreement with the inclusion criteria (Table 2). Lp(a) levels showed a skewed distribution, with median baseline levels of 28.8 and 19.8 mg·DL⁻¹ in the apheresis and medication groups, respectively. The treatment groups were well balanced, and no significant differences were found with respect to baseline characteristics and baseline lipid and lipoprotein concentrations.

Clinical Events and Patient Evaluation

Three patients in the apheresis group and 5 in the medication group had to be hospitalized for unstable angina (Table 3). One of the patients in the apheresis group was lost to follow-up because of death immediately after coronary surgery within 3 months after the start of the study. From the other two patients in the apheresis group with unstable angina, one had to undergo CABG at 9 months after the start of the study and continued only treatment with simvastatin after this procedure; the other one had to undergo a PTCA procedure at 12 months and continued treatment with LDL-apheresis afterward. Four men in the apheresis group had a myocardial infarction, all within 6 months (range, 2 to 6) after the start of the study. In all these patients, LDL-apheresis and simvastatin treatment were continued. Unstable angina in the medication group was observed 5 to 24 months after the start of the study, causing hospitalization and adjustment of antianginal drugs, and two interventions (PTCA and CABG) at the end of the study. A total of seven cardiac events (unstable angina and infarction) in seven different patients in the apheresis group versus five events in five different patients in the medication group was observed (P=.73). Most events took place in the first year of treatment, with a median of 5 versus 5.5 months after the start of the study in the apheresis and medication groups, respectively. There were no significant differences between both groups (Table 3).

Lipid and Lipoprotein Profiles

Three patients in the apheresis group and four in the medication group received additional resin treatment, 8 to 24 g cholestyramine per day. LDL-apheresis caused an acute reduction of 62%, 78%, 71%, and 72% of the mean concentrations of total cholesterol, LDL cholesterol, Lp(a), and apo B, respectively (Table 2). HDL cholesterol levels were not influenced by this procedure, and apo A1 levels were acutely decreased on the average by 20%. Pretreatment levels of total cholesterol, triglycerides, LDL cholesterol, HDL cholesterol, apo A1, and apo B in the apheresis group were not significantly different in comparison to mean levels in the medication group. Pretreatment levels of Lp(a) in the apheresis group did not change compared with basal concentrations, whereas an increase of 15% (P=.03) in the
medication group was found. Differences in treatment effects were established by comparison of interval mean concentrations in the apheresis group and mean concentrations in the medication group. During the entire course of the study, a constant reduction of 63% of LDL cholesterol was found in the apheresis group to an interval mean level of 2.95±1.13 mmol · L⁻¹. Total cholesterol, LDL cholesterol, and apo B showed the same course and were significantly lower in comparison to the medication group (Table 2). HDL cholesterol levels at baseline and during the study were comparable (D) between Apheresis and Medication groups, respectively (multivariate ANOVA).

**Exercise Tests**

Seventeen and 15 pairs of bicycle exercise tests could be evaluated in the apheresis and medication groups, respectively (Table 4). The patient from the apheresis group who died early in the study was excluded from analysis. At baseline, no differences in exercise tolerance by bicycle tests were found between both groups. After 1 year and 2 years of treatment, a significant increment in exercise time; ST-time, time to 1 mm (=0.1 mV) ST depression; ST-max, maximal ST depression; Sbphr-max, systolic blood pressure-heart rate product at maximal exercise; Load-max, maximal load; and Pₐ, Pₜ, and Pₚ, probability values in Apheresis (A) and Medication (M) groups, and of the difference (D) between Apheresis and Medication groups, respectively (multivariate ANOVA).

**Quantitative Analysis of Coronary Angiography**

The coronary angiograms of 20 patients could be evaluated in both groups. The two patients who could not be evaluated at follow-up included one assigned to the apheresis group who underwent CABG surgery and died within 3 months after the start of the study and one assigned to the medication group whose film quality was insufficient for paired analysis. Bypass grafts were included in the analysis: 16 and 22 segments in the apheresis and medication groups, respectively. Paired measurements were available on 351 segments, with a mean of 8.8±2.2 (range, 4 to 15) segments analyzed per patient in both groups. No significant differences were found for the MSD and the MOD between and within the groups analyzed on patient or on segment basis (Table 5). The mean change per patient in percent stenosis was not different for both groups. On a segment basis, the analysis of the changes in percent stenosis showed a comparable reduction in both minor (20% to 50%) and major (>50%) stenotic segments in both treatment groups (Table 5). However, in the apheresis group, the total number of lesions was decreased as the result of the disappearance (<20%) of 40 minor stenoses versus 20 in the medication group (P=.005), whereas 23 versus 32 new stenoses were found, respectively (P=.19). By categorical approach, 9 patients in the apheresis group and 11 patients in the medication group

---

**TABLE 4. Bicycle Exercise Electrocardiography at Baseline, After 1 Year, and After 2 Years of Treatment**

<table>
<thead>
<tr>
<th></th>
<th>Apheresis (n=17)</th>
<th>Medication Only (n=15)</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Test 1</td>
<td>Test 2</td>
<td>Test 3</td>
</tr>
<tr>
<td>Ex-time, s</td>
<td>687±36</td>
<td>687±43</td>
<td>702±41</td>
</tr>
<tr>
<td>ST-time, s</td>
<td>461±47</td>
<td>548±51</td>
<td>641±50</td>
</tr>
<tr>
<td>ST-max, mm</td>
<td>1.4±0.2</td>
<td>0.8±0.2</td>
<td>0.7±0.2</td>
</tr>
<tr>
<td>Sbphr-max, mm/Hg/min</td>
<td>29±44±2020</td>
<td>29±089±1311</td>
<td>29±458±1549</td>
</tr>
<tr>
<td>Load-max, W</td>
<td>151±6</td>
<td>152±7</td>
<td>157±7</td>
</tr>
<tr>
<td>STₐ, mm</td>
<td>27±141</td>
<td>26±090±1015</td>
<td>26±119±1169</td>
</tr>
<tr>
<td>Exₐ, mm</td>
<td>151±10</td>
<td>147±7</td>
<td>151±10</td>
</tr>
</tbody>
</table>

Data are mean±SEM. Tests 1, 2, and 3 indicate exercise test at baseline, after 1 year, and after 2 years of treatment, respectively; Ex-time, maximal exercise time; ST-time, time to 1 mm (=0.1 mV) ST depression; ST-max, maximal ST depression; Sbphr-max, systolic blood pressure-heart rate product at maximal exercise; Load-max, maximal load; and P₀, Pₐ, Pₜ, and Pₚ, probability values in Apheresis (A) and Medication (M) groups, and of the difference (D) between Apheresis and Medication groups, respectively (multivariate ANOVA).
were classified as progressors. Two and 5 patients were regressors, respectively, and the remaining men showed stable disease.

Correlations
Of baseline variables, total cholesterol ($r=-.51$, $P=.01$), LDL cholesterol ($r=-.48$, $P=.02$), ratio of LDL/HDL cholesterol ($r=-.63$, $P=.001$), and apo B ($r=-.49$, $P=.01$) were correlated with time to 0.1 mV ST-segment depression. Relative changes from baseline of total cholesterol and LDL cholesterol were also significantly correlated with the change in time to 0.1 mV ST-segment depression on the exercise ECG (Table 6). No correlations were found between baseline and in-trial lipid and lipoprotein levels and MS or percent stenosis. Only mean in-trial concentrations of total cholesterol, LDL cholesterol, ratio of LDL/HDL cholesterol, and apo B were associated with the percent change in MOD (Table 6 and Fig 2). No correlations were found between time to 0.1 mV ST-segment depression on the exercise ECG and MOD. An association was found between maximal ST depression on the exercise ECG and MOD at baseline ($r=-.48$, $P=.006$) and after 2 years of treatment ($r=-.39$, $P=.03$).

Treatment Side Effects
No significant differences were found between and within the groups for serum creatinine levels, fasting blood glucose, alkaline phosphatase, and leukocyte counts. The patients on apheresis experienced a significant fall in hemoglobin level from 9.2±0.6 mmol·L⁻¹ to 8.6±0.6 mmol·L⁻¹ (−6.0±5.8%) as a result of the procedure. A nonspecific acute loss of 12% of serum protein levels was observed directly after apheresis, without trend in change of pretreatment levels. Twelve of 1039 (1.2%) apheretic procedures were complicated by an episode of hypotension (systolic blood pressure ≤80 mm Hg) not leading to discontinuation of the treatment. No bleeding complications were observed the first days after LDL-apheresis. Only two sessions in 1 patient had to be interrupted due to an "anaphylactoid" reaction caused by the temporary administration of an ACE inhibitor.43,44 During the administration of simva-

### Table 5. Results of Quantitative Computer Analysis of the Coronary Angiographies: Baseline and at the End of the Study

<table>
<thead>
<tr>
<th>Apheresis</th>
<th>Medication Only</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>Baseline</td>
<td>Follow-up</td>
</tr>
<tr>
<td>Per-patient analysis</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Mean segment diameter, mm</td>
<td>2.65±0.49</td>
<td>2.63±0.41</td>
</tr>
<tr>
<td>Minimal obstruction diameter, mm</td>
<td>1.93±0.43</td>
<td>1.92±0.40</td>
</tr>
<tr>
<td>Percent stenosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20%-50%</td>
<td>31.3±5.5</td>
<td>31.9±5.8</td>
</tr>
<tr>
<td>&gt;50%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per-segment analysis</td>
<td>173</td>
<td>178</td>
</tr>
<tr>
<td>Mean segment diameter, mm</td>
<td>2.59±0.96</td>
<td>2.59±0.95</td>
</tr>
<tr>
<td>Minimal obstruction diameter, mm</td>
<td>1.93±0.93</td>
<td>1.92±0.92</td>
</tr>
<tr>
<td>Percent stenosis</td>
<td>177</td>
<td>18</td>
</tr>
<tr>
<td>20%-50%</td>
<td>30.1±7.6</td>
<td>29.6±11.4</td>
</tr>
<tr>
<td>&gt;50%</td>
<td>56.0±7.5</td>
<td>52.5±12.4</td>
</tr>
</tbody>
</table>

Data are mean±SD. Change indicates difference of follow-up minus baseline; P, probability value of treatment effect comparing changes in the apheresis group with the changes in the medication group (t test). In the per-patient analysis, mean percent stenoses >50% were not present.

### Table 6. Correlations Between Lipids and Lipoproteins and Some Outcome Variables, Expressed as Percent Change From Baseline

<table>
<thead>
<tr>
<th>Change from baseline</th>
<th>Change in ST-Time</th>
<th>Change in MOD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
<td>P</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>.42</td>
<td>.04</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>.52</td>
<td>.01</td>
</tr>
<tr>
<td>LDL/HDL ratio</td>
<td>.39</td>
<td>.06</td>
</tr>
<tr>
<td>Apo B</td>
<td>.39</td>
<td>.06</td>
</tr>
<tr>
<td>Mean in-trial concentrations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>−.34</td>
<td>.10</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>−.37</td>
<td>.08</td>
</tr>
<tr>
<td>LDL/HDL ratio</td>
<td>−.30</td>
<td>.15</td>
</tr>
<tr>
<td>Apo B</td>
<td>−.38</td>
<td>.09</td>
</tr>
</tbody>
</table>

Data are mean±SD and are pooled for exercise tests (n=32) and for QCA (n=40). ST-time indicates time to 0.1 mV ST depression on the exercise ECG.

![Fig 2. Correlation between mean in-trial total cholesterol concentration and the change in MOD (a negative value depicts progression).](image)
statin, no subjective adverse experiences were observed. Episodes with aminotransferase levels >3 times the upper limit (≥30 U • L\(^{-1}\)) did not occur: 3 patients in the apheresis group and 1 patient in the medication group had ≥50% of the measurements of alanine aminotransferase (ALAT) between 31 and 99 U • L\(^{-1}\). Creatine phosphokinase (CK) levels were elevated in 3 patients in both groups in ≥50% of the measurements (range, 101 to 468 U • L\(^{-1}\); upper limit of normal ≤100 U • L\(^{-1}\)). None of the patients had to discontinue the administration of simvastatin.

**Discussion**

The LAARS trial was performed to evaluate whether aggressive lipid lowering using LDL-apheresis in men with extensive CAD, of whom the majority had familial hypercholesterolemia (FH), will exert better retardation of the progression of coronary atherosclerosis in comparison to conventional treatment. The study showed that the addition of biweekly LDL-apheresis to lipid lowering treatment with an HMG-CoA reductase inhibitor improved the ischemic threshold, whereas an equal effect in angiographically derived measures for coronary atherosclerosis was observed in both groups, in whom progression of disease would be usual. 43'46

The accepted indication for LDL-apheresis is resistance to drug treatment in patients with CAD. 47 In LAARS, LDL-apheresis was used as a method to lower LDL cholesterol more aggressively in subjects who were not drug resistant. Our results confirm the usefulness of extracorporeal therapy in achieving and maintaining extremely low levels of LDL cholesterol while preserving HDL, with an acceptable safety profile, as has recently been shown. 38'48'49 The reduction of baseline LDL cholesterol from levels of 7.8 mmol • L\(^{-1}\) by 63% in the apheresis group is in keeping with other studies using LDL-apheresis. 22'48'49 On the other hand, LDL reduction from 7.9 mmol • L\(^{-1}\) by 47% in the medication group may be considered a good response in comparison to recent studies using HMG-CoA reductase inhibitors, which is probably the result of frequent monitoring of our patients. 38'48'50'51 Since LDL-apheresis entails a major commitment for the patient and medical community, these latter results stress that only primary hypercholesterolemic patients with established CAD refractory to drug treatment should be treated with LDL-apheresis.

Five prospective trials that include angiographic end points in patients with severe hypercholesterolemia using LDL-apheresis-containing protocols to lower LDL cholesterol have recently been described. 38'48'51 The FH Regression Study 38 and our study are the only randomized ones. Both studies show no further improvement of the angiographic end points by the addition of LDL-apheresis to conventional lipid lowering treatment. However, changes in measures for diffuse atherosclerotic disease (MSD) and focal disease (MOD and % stenosis) in both studies were comparable to pooled data from intervention groups of five recent angiographic regression studies. 5'7'8'10'11 using HMG-CoA reductase inhibitors, as has been described by Thompson et al. 38 Therefore, intermittent LDL reduction by apheresis induces arrest of progression of angiographically visible lesions comparable to drug treatment.

Although LAARS demonstrated a correlation between the change in MOD and mean in-trial concentrations of LDL, it is not clear why further LDL lowering in the apheresis group did not result in more pronounced mean changes in angiographic outcome measures in comparison to the medication group. In contrast to the FH Regression Study, 38 LDL cholesterol levels in the apheresis group from our study were more reduced than in the medication group. In the first study, mean LDL cholesterol levels were 3.2 mmol • L\(^{-1}\) in the apheresis group versus 3.4 mmol • L\(^{-1}\) in the medication group, whereas in our study, levels of 3.0 and 4.1 mmol • L\(^{-1}\) were reached, respectively. The significance of the observed correlation between MOD and in-trial LDL in our study suggests that the nonsustained reduction of LDL cholesterol due to the rebound after LDL-apheresis does not play a role. 38'52 Sample size and the duration of the intervention may be more important, because expected changes in percent stenosis after a relatively short period of intervention have been shown to be too optimistic. 44 Recent data from the Multicentre Anti-Atheroma Study (MAAS) 41 and the Scandinavian Simvastatin Survival Study (4S) 46 support this view. MAAS showed a trend toward improvement, but no statistical differences, of the angiographic measures MOD and MSD after 2 years of simvastatin treatment compared with placebo, whereas after 4 years of treatment significant differences were observed angiographically. 11 The 4S trial showed that the effect of simvastatin treatment on coronary events started after 1 year of therapy and increased steadily thereafter. 10 Therefore, it is not unexpected that differences between the apheresis and medication groups in LAARS were not angiographically detectable.

The reduction of time-averaged levels of Lp(a) in the apheresis group from that in LAARS was much less in comparison to LDL. This may be caused by an increase of Lp(a) concentrations associated with the administration of simvastatin, which was also found in the medication group, and has been confirmed by others. 38'53 However, an increased rebound of Lp(a) after apheresis in comparison to LDL may also play a role. 31'54 One of the objectives of the FH Regression Study 38 was to verify whether lowering of Lp(a) concentrations by apheresis was associated with further reduction of the percent diameter stenosis of coronary arteries. No benefit could be shown of reducing Lp(a) levels in patients whose LDL cholesterol levels had been effectively lowered by drug therapy or apheresis. Our data confirm these results, particularly because the differences in mean in-trial LDL cholesterol concentrations in the medication and apheresis groups were greater than those in the FH Regression Study, with comparable changes in Lp(a) levels in both studies. So, the question of the clinical relevance of increased Lp(a) levels during treatment with an HMG-CoA reductase inhibitor seems current.

Naturally occurring progression of CAD is mainly seen in the formation of new coronary lesions and less in growth of preexisting ones, and progression of the latter is correlated with high cholesterol levels. 46 Most regression studies showed the greatest benefit in atheroma obstructing >50% of the lumen, 13 and some reported that mainly smaller lesions responded. 5'11'55 In the present study, percent stenosis remained almost unchanged during the 2 years of treatment (97% of stenoses showed changes in degree of ≤20%), and no preference for changes in severe (>50%) stenoses was observed. It was found, however, that more aggressive lipid lowering with LDL-apheresis resulted in the disappearance of more...

---

**Vol 93, No 10 May 15, 1996**

---
mild to moderate (20% to 50%) lesions, whereas the formation of new lesions appeared to be comparable between the apheresis and medication groups. Therefore, our data appear to be in favor of reducing more early lesions as a response to aggressive lipid lowering of relatively short duration, as has also been shown in the Canadian Coronary Atherosclerosis Intervention Study (CCAIT) and MAAS. This may be important, since early lipid-rich lesions with a fine fibrous cap are prone to rupture and lead to thrombotic occlusions and consequent clinical events. Therefore, more aggressive lipid lowering appears to improve stabilization and regression of these lesions.

A remarkable observation of our study was the improvement in ergometric bicycle tests. This has also been found in some uncontrolled studies while applying LDL-apheresis and may be present within weeks from the start of treatment. We observed significant improvement of the exercise tests after 1 year of treatment, which further increased after 2 years. Changes in the time to 0.1 mV ST depression after 2 years of treatment were also significantly correlated with the amount of LDL reduction. These findings and the angiographic ones suggest that mechanisms other than changes in stenosis play a role in the outcome of the exercise tests. Indeed, cholesterol lowering with HMG-CoA reductase inhibitors has been shown to improve endothelium-dependent relaxation in the coronary arteries of patients with atherosclerosis. On the other hand, improved blood flow by changes in blood rheology induced by LDL-apheresis may also contribute to the improvement of coronary flow. However, reductions of fibrinogen and most other coagulation factors do not last longer than 24 to 48 hours, whereas changes in blood viscosity have been measured until 1 week after an apheresis using dextran sulfate adsorption. Since the follow-up assessments at the end of the study in LAARS were done 3 to 4 weeks after the last LDL-apheresis, rheological changes did not confound our results. This indicates that functional improvements of the coronary vasomotor function on a level beyond the resolution of the angiogram may precede anatomic changes in severely stenotic coronary arteries. Therefore, functional measures should be considered as additional and possibly more sensitive outcome variables for short-term angiographic studies. In our study, we also assessed the videodensitometric measurements of the blood flow in the coronary microcirculation as a functional primary outcome variable. These data are presently being analyzed and will be published separately.

It has been shown that culprit lesions in unstable angina have increased vasoreactivity, which is responsible for the risk of recurrence of unstable angina or infarction. Plaque stabilization by lipoprotein manipulation may require more than 1 year of aggressive treatment before a significant reduction in clinical events can be documented. In our study, we were confronted with a few myocardial infarctions in the apheresis group in the early phase of the study, a difference with the medication group that may be associated with the use of anticoagulants or platelet aggregation inhibitors. It must be emphasized that our study was not designed to evaluate the clinical events. However, in combining both episodes of unstable angina and myocardial infarctions, no differences between both treatment groups were observed. Considering the natural progression of CAD, it is notable that both treatment groups showed less events than expected in the second year of treatment. This observation supports the notion that the effect of cholesterol lowering on functional improvement precedes anatomic regression of atherosclerosis.

Conclusions

Combined LDL-apheresis and cholesterol lowering drugs in patients at high risk for cardiovascular events arrests further progression of CAD and induces functional improvement of the coronary blood flow. Studies of longer intervention periods are warranted to confirm these findings and observe the expected angiographic regression of CAD. However, only primary hypercholesterolemic patients with established CAD refractory to drug treatment should be treated with LDL-apheresis.

Acknowledgments

This study was supported by the Dutch Heart Foundation (grant 90.065). Simvastatin was provided by Merck Sharp & Dohme BV, Haarlem, the Netherlands, whose financial support is also acknowledged. The separators, adsorption columns, and other disposables for the apheresis unit were provided at reduced cost by Kaneka Deutschland GmbH, Wiesbaden, Germany. The authors wish to thank the nursing staff of the apheresis unit, the laboratory personnel, and Mrs D. Kampshure, who participated as a research nurse, for their excellent assistance.

References

monotherapy with an HMG-CoA reductase inhibitor on the pro-
gression of coronary atherosclerosis as assessed by serial quanti-
tative arteriography: the Canadian Coronary Atherosclerosis In-

11. MAAS Investigators. Effect of simvastatin on coronary atheroma:
the Multicentre Anti-Atheroma Study (MAAS). Lancet. 1994;344:

Zwinderman AH, Jansen H, Boerma GM, van Rappart FM, Lie
KI, on behalf of the REGRESS Study Group. Effects of lipid
lowering by pravastatin on progression and regression of coronary
atherosclerotic disease in men with normal to moderately
-elevated serum cholesterol levels: the Regression Growth Eval-

13. Blankenhorn DH, Hodis HN. George Lyman Duff Memorial
Lecture: Arterial imaging and atherosclerosis reversal. Arterio

14. Brown BG, Zhao X-Q, Sacco DE, Albers JJ. Lipid lowering and
rupture and clinical events in coronary disease. Circulation. 1993;87:
1781-1791.

15. Superko HR, Krauss RM. Coronary artery disease regression:
convincing evidence for the benefit of aggressive lipoprotein man-

16. Scandinavian Simvastatin Survival Study Group: randomised tri-
all of cholesterol lowering in 4444 patients with coronary heart
1994;344:1383-1389.

17. Yokoyama S, Hayashi R, Satani M, Yamamoto A. Selective
removal of low density lipoproteins by phasemixing in familial

lipoprotein apheresis system using two dextran sulfate cellulose
columns in an automated column regenerating unit (LDL con-

19. Thompson GR, Miller JP, Breslow JL. Improved survival of patients
with homozygous familial hypercholesterolemia treated by plasma

20. Koga N, Iwata Y. Pathological and angiographic regression of
chordate plugging and plaque regression. New insights into prevention of plaque
disruption and clinical events in coronary disease. Circulation. 1993;87:
1781-1791.

21. Koga N, Iwata Y. Pathological and angiographic regression of
chordate plugging and plaque regression. New insights into prevention of plaque
disruption and clinical events in coronary disease. Circulation. 1993;87:
1781-1791.

22. Yamamoto A. Regression of atherosclerosis in humans by lowering
low density lipoprotein apheresis system using two dextran sulfate cellulose
columns in an automated column regenerating unit (LDL con-

23. Thompson GR, Miller JP, Breslow JL. Improved survival of patients
with homozygous familial hypercholesterolemia treated by plasma

lipoprotein apheresis system using two dextran sulfate cellulose
columns in an automated column regenerating unit (LDL con-

25. Thompson GR, Miller JP, Breslow JL. Improved survival of patients
with homozygous familial hypercholesterolemia treated by plasma

26. Brown BG, Zhao X-Q, Sacco DE, Albers JJ. Lipid lowering and
rupture and clinical events in coronary disease. Circulation. 1993;87:
1781-1791.

27. Levine GN, Keaney JF, Vita JA. Cholesterol reduction in cardio-

28. Stalenhofen AFH, Mol MJTM, Stuyt PMJ. Efficacy and tolerability
of pravastatin therapy in patients with heterozygous familial hyperchole-
sterolemia: implications for clinical trials. Circulation. 1993;87(suppl II):
11-38-147.

29. Levine GN, Keeney JF, Vita JA. Cholesterol reduction in cardio-

30. Stalenhofen AFH, Mol MJTM, Stuyt PMJ. Efficacy and tolerability
of pravastatin therapy in patients with heterozygous familial hyperchole-
sterolemia: implications for clinical trials. Circulation. 1993;87(suppl II):
11-38-147.

31. Levine GN, Keeney JF, Vita JA. Cholesterol reduction in cardio-

32. Stalenhofen AFH, Mol MJTM, Stuyt PMJ. Efficacy and tolerability
of pravastatin therapy in patients with heterozygous familial hyperchole-
sterolemia: implications for clinical trials. Circulation. 1993;87(suppl II):
11-38-147.

33. Levine GN, Keeney JF, Vita JA. Cholesterol reduction in cardio-

34. Stalenhofen AFH, Mol MJTM, Stuyt PMJ. Efficacy and tolerability
of pravastatin therapy in patients with heterozygous familial hyperchole-
sterolemia: implications for clinical trials. Circulation. 1993;87(suppl II):
11-38-147.


