Long-Term Effect of Low-Density Lipoprotein Apheresis on Plasma Lipoproteins and Coronary Heart Disease in Native Vessels and Coronary Bypass in Severe Heterozygous Familial Hypercholesterolemia

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Low-density lipoprotein (LDL) apheresis is a potent treatment for patients with coronary heart disease and severe hereditary forms of LDL hypercholesterolemia not adequately responsive to drug treatment. Until now, the beneficial effect of aggressive reduction of LDL cholesterol by LDL apheresis on the course of coronary heart disease has been demonstrated in one 3-year study and several studies lasting 2 years. We now report on the clinical course, lipoprotein concentrations, coronary angiograms, and side effects in patients undergoing LDL apheresis for as long as 8.6 years. Thirty-four patients (21 men and 13 women) with coronary heart disease and heterozygous familial hypercholesterolemia (FH) not adequately responsive to lipid-lowering drugs received weekly (four patients biweekly) LDL apheresis for 4.6 ± 2.6 years under diet and lipid-lowering drug therapy; after 0.5 to 3 years, simvastatin in the maximal tolerable dose was added. The baseline LDL cholesterol concentration was 6.9 ± 1.6 mmol/L. Combined treatment in the steady state yielded a pretreatment and posttreatment LDL cholesterol concentration of 4.8 ± 0.9 and 1.8 ± 0.4 mmol/L, respectively. The calculated interval mean LDL cholesterol was 3.3 ± 0.6 mmol/L. Evaluation of the coronary angiographies revealed a definite regression of coronary lesions in four patients (11.8%); in 19 patients, there was a cessation of progression. Two patients developed atheromatous lesions in bypass grafts (L.H., 60% stenosis; S.M., occlusion). Of 23 patients elegible for the scoring of anginal symptoms, five (21.7%) reported a reduction of the frequency and severity of angina pectoris. The mean coronary symptom score in 23 patients changed from 1.65 ± 0.83 at baseline to 1.39 ± 0.66 at the end of the study. During the whole observation period, we observed three sudden deaths, one nonfatal myocardial infarction, and five patients requiring hospital admission because of unstable angina pectoris, one of which was followed by a transluminal coronary angioplasty. Aggressive reduction of LDL cholesterol with combined LDL apheresis and drugs induced regression of coronary lesions in four of 34 patients and prevented progression in 29 patients for as long as 8.6 years. The effect on LDL and high-density lipoprotein (HDL) cholesterol and lipoprotein(a) [Lp(a)] was comparable with all three apheresis techniques. Therefore, no obvious difference between the three techniques was found regarding changes in coronary lesions.

FAMILIAL HYPERCHOLESTEROLEMIA (FH) is known to be associated with a high risk to develop severe atherosclerosis, in particular coronary lesions, at an early age. Before the era of hepatic hydroxymethyl glutaryl coenzyme A (HMG-CoA) reductase inhibitors, male heterozygous carriers had a 52% probability of clinically apparent coronary heart disease.[1] Homozygous individuals may even present with myocardial infarction in childhood or adolescence.[2,3] Meanwhile, several intervention studies have demonstrated that an extensive decrease of low-density lipoprotein (LDL) cholesterol with combined hypolipidemic drugs may reduce the incidence of cardiovascular events in patients with nonfamilial LDL hypercholesterolemia and coronary heart disease, and may prevent the progression of coronary atherosclerotic lesions.[4-8] A LDL cholesterol concentration of 2.5 to 3.0 mmol/L is regarded as necessary to reach this goal.[4-6] However, in a proportion of patients with FH, even combined drug treatment may fail to reach this goal by a large margin. These individuals are undoubtedly at high risk of rapid progression of coronary lesions.

LDL apheresis has been designed as a potent additional therapy for treating patients with severe hereditary forms of hypercholesterolemia. The three most commonly applied techniques are immunoadsorption,[9,10] heparin-induced extracorporeal LDL precipitation (HELP),[11,12] and dextran sulfate adsorption.[13,14] These methods have been proved as safe and effective forms of treatment. If applied in combination with drugs, the mean LDL cholesterol level can be decreased to 20% of the initial concentration.[15]

Several groups have addressed the issue as to whether LDL apheresis treatment can also positively influence the course of coronary heart disease in patients with FH. Angiographically controlled regression studies have shown that coronary atherosclerosis can be stabilized, and even regression can be induced, during a treatment period of 2 years[16-19] to 3 years.[20] We now present data on 34 patients with heterozygous FH and angiographically proven coronary heart disease on LDL apheresis for as long as 8.6 years. The long-term lipoprotein changes, clinical disease course, and results of coronary angiography performed at 2-year intervals will be discussed.

SUBJECTS AND METHODS

Patients and Study Design

Thirty-four patients (21 men and 13 women) with heterozygous FH were included in the study. The diagnosis of FH was made on the basis of a positive family history of severe hypercholesterolemia, angiographically proven early-onset coronary heart disease, and failure to respond sufficiently to any of the currently available drugs. Despite a specific cholesterol-lowering diet (300 mg cholesterol/d; 30% of daily energy intake as fat, with 10% each of saturated, monounsaturated, and polyunsaturated fatty acids) and vigorous combined hypolipidemic drug treatment with agents such as anion-exchange resins, fibrates, nicotinic acid, and HMG-CoA reductase inhibitors, LDL cholesterol concentrations were not decreased sufficiently. Twenty-nine patients

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presented a LDL cholesterol concentration greater than 4.7 mmol/L, and five had levels of 4.7 mmol/L or less. Eighteen patients received immunoadsorption, eight HELP apheresis, and eight dextran sulfate adsorption. In all but four patients, treatments were performed weekly. The remaining four patients, all with only a moderate reincrease in LDL cholesterol between two LDL aphereses (LDL cholesterol < 2.6 mmol/L 1 week after treatment), were placed on a fortnightly schedule. To evaluate the efficacy of LDL apheresis alone, all lipid-lowering drugs were withdrawn for the initiation of treatment. Eight patients on immunoadsorption were additionally treated with simvastatin at the maximal tolerable dose after 3 years of treatment, five patients on HELP apheresis after 2 years, and six patients on dextan sulfate adsorption after 6 months (due to study protocols for evaluating the procedures). All other patients received simvastatin from the beginning of LDL apheresis. The different periods were due to different study protocols used for the initial evaluation of LDL apheresis. Nineteen patients received simvastatin 40 mg/d, one patient 30 mg/d, and seven patients 20 mg/d. Six patients discontinued taking a HMG-CoA reductase inhibitor because of subjective side effects (myalgia without elevation of creatine kinase or arthralgia). Patients also were required to refrain from smoking. They were allowed to miss four treatments per year.

LDL Apheresis

Patients were treated with either immunoadsorption, HELP apheresis, or dextran sulfate adsorption. Procedures were performed as previously described (immunoadsorption,[9] HELP apheresis,[11] and dextran sulfate adsorption[14]).

Laboratory Analyses

Blood samples were drawn at the onset and termination of every procedure for the determination of total cholesterol, triglycerides, high-density lipoprotein (HDL) cholesterol, LDL cholesterol (calculated according to the Friedewald formula), full blood cell count, total protein, prothrombin time, partial thromboplastin time, and electrolytes. Liver function and lactate dehydrogenase activity were determined monthly. Renal function, blood glucose, magnesium, creatine kinase, uric acid, ferritin, transferrin, haptoglobin, and urinalysis were determined every 3 months.

Total cholesterol and triglycerides were determined enzymatically in duplicate (Boehringer, Mannheim, Germany) on an automated analyzer (Epos; Eppendorf, Hamburg, Germany). The HDL cholesterol level was measured enzymatically after precipitation of apolipoprotein B–containing lipoproteins with sodium phosphotungstate and $MgCl_2$ (Boehringer).

Lipoprotein(a) [Lp(a)] was determined by radioimmunoassay (Pharmacia, Freiburg, Germany). The interval mean for LDL cholesterol between the two treatments was calculated as the mean of the pretreatment and posttreatment concentrations. As shown before, the reincrease of LDL cholesterol is linear during the first week following LDL apheresis.[9] Patients on fortnightly therapy had a flatter reincrease during the first week. The interval mean for Lp(a) was calculated in the same way.

Safety parameters were analyzed by routine clinical chemistry methods. All results are expressed as the mean ± SD. In the case of Lp(a), the median value is given. The *U* test (Mann-Whitney) was applied to examine statistical differences.

Coronary Angiography

Coronary angiography was performed at baseline and subsequently every 2 years. Three experts working independently estimated the global change score of blinded films demonstrated in a random sequence. The films were recorded in the 30° RAO and 60° LAO position. All coronary lesions of every film and changes in lesions on subsequent films were marked in predrawn diagrams of coronary arteries. According to the most advanced lesion of an angiogram, the severity of coronary heart disease was graded from I to IV, where I represents a maximum stenosis less than 50%, II a 50% to 75% stenosis, III a 75% to 99% stenosis, and IV an occlusion. Bypass grafts were judged accordingly. After revision of all films from a patient, a global change score as used in the Cholesterol Lowering Atherosclerosis Study (CLAS) was applied to the sequence of films: 0, no demonstrable change; 1, definitely discernible change; 2, intermediate change; and 3, extreme change.[4] When the temporal order of the films was displayed, a sequence of films showing progression was assigned a "+," and a sequence showing regression a "−." The final judgment was based on a consensus of all investigators as to the baseline findings, change in stenoses, and global change score.

Clinical Judging

At completion of the study, patients who still underwent LDL apheresis and had not undergone any coronary revascularization procedure were asked to complete a score on the severity and frequency of angina pectoris at baseline and at completion of the study. The judging was performed using the following coronary symptom score: 1, no angina; 2, angina at severe exertion; 3, angina at minor exertion; and 4, angina at rest.

RESULTS

Clinical Characteristics

Thirty-four patients (21 men and 13 women) aged 47 ± 9 years underwent regular LDL apheresis. The mean treatment period was 4.6 ± 2.6 years (range, 8.6 to 0.9); six patients were treated longer than 8 years, 10 longer than 6 years, and 18 longer than 3 years. Clinical characteristics at baseline are summarized in Table 1. In addition to FH, nine patients had hypertension. One patient developed non–insulin-dependent diabetes mellitus 8 years after entering the study, which was well controlled with dietary measures. Patients with hypertension received medication to reduce the blood pressure to less than 140/90 mm Hg. By the time they entered the study, 11 patients had suffered a myocardial infarction, 12 had undergone bypass surgery, and five had a transluminal coronary angioplasty. Twenty patients complained of stable angina when entering the study.

During the observation period, there were three sudden deaths (one patient on immunoadsorption and two patients on HELP) after 6 and 9 months and after 6 years of therapy, respectively. None of these events were related to the treatment procedure. In none of these patients could an autopsy be performed; however, the clinical course suggests an underlying cardiovascular cause, eg, myocardial infarction, arrhythmia, or pulmonary embolism. Shortly after beginning LDL apheresis, one patient had a bypass graft, and another a transluminal coronary angioplasty. However, both interventions were already

Table 1. Clinical Characteristics at Baseline (N = 34)

Characteristic	No.	%
Age (mean ± SD)	47 ± 9	
Sex ratio (men/women)	21/13	
Hypertension	9	26.5
Diabetes mellitus	1	2.9
Previous myocardial infarction	11	32.3
Previous bypass surgery	12	35.3
Stable angina pectoris	20	58.8

planned before commencing LDL apheresis. In another patient, the occasion of an aortic valve replacement was used to graft a high-degree coronary stenosis. We observed one nonfatal myocardial infarction in a patient (on dextran sulfate adsorption) who had an occlusion of one bypass graft. There were five patients requiring hospital admission because of unstable angina pectoris during the observation period, one of which was followed by a transluminal coronary angioplasty.

Lipoprotein Concentrations

Before commencing LDL apheresis, on dietary and drug therapy, the patients presented a mean LDL cholesterol concentration of 6.9 ± 1.6 mmol/L. HDL cholesterol and triglycerides were 1.0 ± 0.3 and, 2.0 ± 1.4 mmol/L, respectively. The median Lp(a) level was 58 ± 48 mg/dL. Under regular LDL apheresis, patients had similar pretreatment and posttreatment lipoprotein concentrations, ie, they were in steady state. Therefore, the mean concentrations of lipoproteins for five subsequent regular treatments of all patients were taken as a representative sample for the concentrations attained under regular LDL apheresis and simvastatin. For lipoprotein concentrations before and after apheresis, total cholesterol, LDL cholesterol, and Lp(a), interval means are presented (Table 2). Compared with the concentrations before apheresis, there was an overall decline in LDL cholesterol from 6.9 ± 1.6 mmol/L to an interval mean of 3.3 ± 0.6 mmol/L (Table 3). Lp(a) decreased from 58 ± 48 mg/dL to 25 ± 34 mg/dL, and HDL cholesterol increased 25.0% from 1.0 ± 0.3 mmol/L to 1.3 ± 0.2 mmol/L. The decrease of LDL cholesterol and Lp(a), as well as the increase, were comparable with all three apheresis techniques. The concomitant decline in LDL cholesterol and increase in HDL cholesterol caused the LDL/HDL cholesterol ratio to decrease from 6.5 to 2.6. In the steady state, 11 patients still had a mean LDL cholesterol (mean of pretreatment and posttreatment concentration of the last five treatments) higher than 3.4 mmol/L, five between 3.1 and 3.4 mmol/L, seven between 2.9 and 3.1 mmol/L, eight between 2.6 and 2.9 mmol/L, and three less than 2.6 mmol/L.

Table 2. Effects of LDL Apheresis on Serum Lipoproteins (mmol/L; mg/dL for Lp(a); mean ± SD of 5 treatments in steady state)

Parameter	Before Apheresis	After Apheresis	Mean Value Between 2 Apheresis
All procedures (n = 34)			
Total cholesterol	6.9 ± 1.1	3.3 ± 0.6	5.0 ± 0.9
Triglycerides	1.9 ± 1.1	1.0 ± 0.8	
HDL cholesterol	1.3 ± 0.2	1.1 ± 0.2	
LDL cholesterol	4.8 ± 1.0	1.8 ± 0.4	3.3 ± 0.6
Lp(a)*	33 ± 50	17 ± 19	25 ± 34
Immunoadsorption (n = 18)			
Total cholesterol	6.9 ± 1.3	3.3 ± 0.6	5.1 ± 0.9
Triglycerides	1.8 ± 1.3	1.0 ± 0.8	
HDL cholesterol	1.3 ± 0.3	1.1 ± 0.2	
LDL cholesterol	4.7 ± 1.0	1.8 ± 0.4	3.2 ± 0.6
Lp(a)*	35 ± 18	17 ± 9	26 ± 13
HELP (n = 8)			
Total cholesterol	7.1 ± 0.7	3.6 ± 0.6	5.4 ± 0.5
Triglycerides	1.8 ± 0.5	1.0 ± 0.4	
HDL cholesterol	1.2 ± 0.2	1.0 ± 0.2	
LDL cholesterol	5.1 ± 0.8	2.1 ± 0.6	3.6 ± 0.5
Lp(a)*	96 ± 20	31 ± 12	63 ± 16
Dextran sulfate adsorption (n = 8)			
Total cholesterol	7.0 ± 1.0	3.2 ± 0.5	5.0 ± 1.1
Triglycerides	2.1 ± 1.2	1.2 ± 0.9	
HDL cholesterol	1.2 ± 0.2	1.0 ± 0.2	
LDL cholesterol	4.9 ± 1.1	1.7 ± 0.4	3.3 ± 0.7
Lp(a)*	35 ± 21	18 ± 8	27 ± 18

*Median ± SD.

Table 3. Long-Term Effects of Regular LDL Apheresis on Serum Lipoproteins (mmol/L; mg/dL for Lp(a))

Parameter	Before First Apheresis Under Diet + Lipid-Lowering Drugs	Mean of Last 5 Treatments
All procedures (n = 34)		
Total cholesterol	8.1 ± 2.7	5.1 ± 0.9
Triglycerides	2.0 ± 1.4	1.9 ± 1.1
HDL cholesterol	1.0 ± 0.3	1.3 ± 0.2
LDL cholesterol	6.7 ± 1.6	3.3 ± 0.6
Lp(a)*	58 ± 48	25 ± 34
Immunoadsorption (n = 18)		
LDL cholesterol	6.7 ± 1.4	3.2 ± 0.6
HDL cholesterol	1.0 ± 0.3	1.3 ± 0.3
Lp(a)*	54 ± 42	26 ± 13
HELP (n = 8)		
LDL cholesterol	6.6 ± 1.4	3.6 ± 0.5
HDL cholesterol	1.0 ± 0.2	1.2 ± 0.2
Lp(a)*	132 ± 43	63 ± 16
Dextran sulfate adsorption (n = 8)		
LDL cholesterol	6.0 ± 0.2	3.3 ± 0.7
HDL cholesterol	1.0 ± 0.2	1.2 ± 0.2
Lp(a)*	48 ± 34	27 ± 15

*Median ± SD.

Coronary Angiography

The long-term results of the global coronary score for 23 patients evaluated for more than 2 years are shown in Table 4. In four patients, we observed a regression of coronary atherosclerosis (a definitely discernible regression in three patients and an intermediate regression in one patient); in all other cases, progression of coronary lesions ceased (no change), in particular, there was no case of occlusion of native coronary stenoses. Regression occurred at 2 (L.B. and S.J.), 4 (R.D.), and 6 (W.F.) years after commencing LDL apheresis. Table 5 summarizes the global change score of the bypass vessels in 13 patients. After 2 and 4 years, respectively, two patients had a progression of atherosclerosis in these vessels, one of whom, 2 years after beginning LDL apheresis, presented with an occlusion and subsequent myocardial infarction. When comparing lipoprotein concentrations in patients showing angiographic progression with nonprogressors, we found higher pretreatment (6.1 ± 0.5 *v* 4.7 ± 0.9 mmol/L) and interval mean LDL cholesterol concentrations (4.1 ± 0.3 *v* 3.2 ± 0.6 mmol/L).

Table 4. Global Change Score of Coronary Arteries Under LDL Apheresis

Patient Initials	Sex/ Age (yr)	Vessels Affected	Severity	Duration of Treatment (yr)	Global Change Score
Immunoadsorption					
K.K.	F/43	1	II	8.4	0
R.C.	F/44	3	IV	8.3	0
R.D.	M/29	3	III	8.2	−1
W.F.	M/37	3	IV	7.5	−1
S.B.	F/43	2	II	7.5	0
S.P.	M/46	1	IV	7.3	0
M.A.	F/58	3	IV	6.2	0
T.W.	M/33	3	III	5.1	0
S.J.	M/52	3	IV	4.2	0
H.E.	F/52	3	III	3.2	0
W.K.	M/49	3	IV	2.6	0
S.K.	F/60	3	III	2.5	0
S.B.	F/49	2	I	2.5	0
K.K.	F/64	3	II	2.0	0
F.E.	F/55	3	IV	1.9	ND
T.L.	M/41	2	IV	1.8	ND
H.A.	M/35	1	I	1.7	ND
A.W.	M/47	3	IV	0.9	ND
HELP					
L.H.	F/44	3	IV	8.6	0
B.F.	M/38	3	III	8.5	0
S.J.	M/47	3	I	8.3	−2
L.B.	F/56	3	II	5.4	−1
R.W.	M/50	1	III	2.2	0
S.B.	M/49	3	IV	1.2	ND
S.G.	M/36	3	III	1.8	ND
M.F.	M/29	3	III	1.0	ND
Dextran sulfate adsorption					
Z.A.	M/62	2	IV	3.3	0
B.A.	M/49	2	II	3.2	0
S.H.	F/50	2	II	3.2	0
K.E.	M/54	3	III	3.1	0
S.M.	M/45	3	IV	2.6	0
B.W.	M/50	2	II	2.2	0
M.F.	M/29	3	III	1.0	ND
M.G.	F/30	3	II	0.9	ND

Abbreviation: ND, not determined.

Clinical Judging

At the baseline of the study, 14 patients did not present coronary symptoms (after bypass surgery or myocardial infarction), and nine complained of angina at severe exertion, ten at moderate exertion, and one at rest. Of the patients who did not receive any revascularization procedures, 23 were available for the clinical judging before leaving the study. Of these patients, five (S.J., W.K., W.F., L.H., and M.G.) reported a reduction of the frequency and severity of angina. Of the four patients with angiographically proven regression of coronary heart disease, three (L.B., S.J., and R.D.) never presented with angina pectoris during the study; W.F. reported a change in the coronary symptom score from 2 to 1. The mean coronary score was 1.65 ± 0.83 at baseline and 1.39 ± 0.66 at completion ($n = 23$). The exact period of symptom improvement could not be stated in most instances; however, symptoms were relieved within the first few months after commencing LDL apheresis in all cases.

Adverse Events, Technical Pitfalls, and Safety Parameters

A total of 5,575 LDL apheresis treatments were performed (immunoadsorption, 3,499; HELP apheresis, 1,497; and dextran sulfate adsorption, 579). In 299 instances (5.4%), the treatment procedure had to be interrupted ($n = 258$) or could not be performed ($n = 51$, 0.9%). Of these treatments, 198 (3.6%) were caused by technical pitfalls and 101 (1.8%) by adverse clinical events (92 by problems with venous access). In five instances, 5% albumin solution had to be administered to treat hypotension that could not be reversed by infusion of normal saline. In general, the adverse reactions were usually mild and easily reversible by minor symptomatic treatment. Apart from a moderate decrease in hemoglobin and ferritin levels, there were no clinically relevant long-term changes in any safety parameter. Patients who developed subnormal ferritin levels were given oral or, if not tolerated, intravenous iron supplementation.

DISCUSSION

The present study summarizes the long-term clinical, laboratory, and coronary angiography results of patients with hereditary forms of hypercholesterolemia and coronary heart disease treated with regular LDL apheresis. The primary aim of the study was to evaluate whether the positive short-term effects of aggressive lipid-towering therapy by LDL apheresis on exercise tolerance and coronary lesions could be preserved during long-term follow-up study. LDL apheresis produced an acute decline of 62.6% and 48.5% in the mean concentration of LDL cholesterol and Lp(a), respectively. Compared with combined dietary and drug therapy with a mean LDL cholesterol concentration of 6.9 ± 1.6 mmol/L, the interval mean achieved under LDL apheresis was 3.3 ± 0.6 mmol/L (Table 3). No difference was observed between the three apheresis techniques in the effects on plasma lipoproteins. Regression of coronary artery disease was observed in 11.8% of patients. The results of the coronary symptom score suggest that also patients (17.4%) whose coronary angiography did not change showed improvement in exercise tolerance in daily practice.

There have been five angiographically controlled intervention trials applying LDL apheresis in severe hereditary forms of hypercholesterolemia. Borberg and Oette[20] were the first to

Table 5. Global Change Score of Coronary Bypasses

Patient Initials	Sex/ Age (yr)	No. of Bypasses	Duration of Treatment (yr)	Global Change Score
L.H.	F/44	3	8.4	+1
R.C.	F/44	2	8.3	0
S.B.	F/43	1	7.5	0
W.F.	M/37	2	7.3	0
M.A.	F/58	2	6.2	0
T.W.	M/33	2	5.1	0
S.J.	M/52	2	4.0	0
S.K.	M/60	3	2.5	0
W.K.	M/49	2	2.4	0
S.M.	M/45	2	2.4	+3
Z.A.	M/45	2	2.4	0
T.L.	M/41	1	1.8	ND
A.W.	M/47	3	0.9	ND

Abbreviation: ND, not determined.

demonstrate the beneficial effect of immunoadsorption used without lipid-lowering drugs on the course of coronary heart disease. The patients investigated (initial total cholesterol > 13.0 mmol/L) presented a mean interval LDL cholesterol concentration of 4.3 mmol/L during therapy. Five of 74 evaluated stenoses progressed and 69 remained stable after 3 years of therapy. Schuff-Werner et al[16] investigated the effect of combining lipid-lowering drugs and weekly HELP apheresis therapy on lipoproteins and coronary heart disease in 39 patients during a 2-year period. Thirty-three patients whose coronary angiography results could be analyzed had an initial mean LDL cholesterol of 6.9 ± 1.7 mmol/L; during therapy, the mean pretreatment and posttreatment concentrations were 5.2 ± 1.0 and 2.1 ± 0.5 mmol/L, respectively. The 187 segments evaluated showed a regression greater than 8% in 26.7% of stenoses, stability in 57.8%, and progression in 15.5%. Tatami et al[17] presented similar results in a 2-year study of 37 patients (both homozygous and heterozygous FH) with an initial LDL cholesterol concentration of 13.0 ± 0.8 and 8.1 ± 2.3 mmol/L, respectively. Various apheresis regimens (weekly, fortnightly, and 4-weekly) combined with probucol or pravastatin yielded a pretreatment and posttreatment LDL cholesterol of 10.0 ± 2.0 and 2.7 ± 0.6 mmol/L in homozygous and 4.9 ± 1.5 and 1.8 ± 0.6 mmol/L in heterozygous patients. Regression, defined as a change in a stenosed segment greater than 11.2%, was observed in 37.8% of patients, stable lesions in 48.6%, and progression of coronary heart disease in 13.5%.

There have also been two randomized trials comparing LDL apheresis with hypolipidemic drug treatment. Thompson et al[18] compared two groups receiving either fortnightly LDL apheresis by dextran sulfate adsorption and simvastatin (n = 20) or simvastatin and colestipol (n = 19) for a period of 2 years. The mean LDL cholesterol of the drug-treated group and the interval mean LDL cholesterol of the apheresis group did not differ significantly. Mean LDL cholesterol concentrations before and after apheresis were 4.15 and 1.4 mmol/L, respectively. Coronary angiography at 2 years did not show any significant changes in the angiographic endpoints investigated.[18] More recently, Kroon et al[19] compared the combination of simvastatin and LDL apheresis by dextran sulfate adsorption (n = 21) with simvastatin only (n = 21) in a 2-year study. Treatment with simvastatin yielded a mean LDL cholesterol of 4.1 mmol/L, whereas LDL apheresis resulted in a significantly lower interval mean LDL cholesterol of 3.0 mmol/L. Exercise tolerance was significantly greater in the apheresis group after 1 and 2 years; however, the clinical events and results on coronary angiography, were not significantly different between the groups.

The lipoprotein concentrations reached in the present study are in good agreement with results of the previous studies,[16-18] although in one study a greater reduction in LDL cholesterol was achieved.[19] This was due to relatively low pretreatment and posttreatment concentrations of LDL cholesterol. In contrast to other studies,[18,19] we selected only patients not tolerating lipid-lowering drugs or not adequately responding to drug treatment. Kroon et al noted in their study that LDL apheresis was used as a means to aggressively decrease LDL cholesterol in patients who had responded to drugs. We also presume that in the study by Thompson et al the patients on LDL apheresis also could have been treated with drugs only, as fortnightly LDL apheresis in all subjects resulted in a reasonable lipoprotein profile and the control group showed a good response to drug treatment. Better results regarding the cardiovascular endpoints in the patient group therefore could not be expected. For these patients, selected LDL apheresis may not have been superior to drug therapy; however, this is not true for the patients investigated in this study. Most of our patients had a particularly severe form of FH indicated by a mean LDL cholesterol concentration of 6.9 ± 1.6 mmol/L before starting LDL apheresis. In 31 of these cases (91.2%), even weekly treatment did not decrease the interval mean LDL cholesterol level to less than 2.6 mmol/L, which would be ideal according to the results of various other regression studies.[4-8] However, we think that LDL apheresis is the treatment of choice, especially for these patients. The two randomized LDL apheresis studies achieved sufficient interval mean concentrations of LDL cholesterol with a fortnightly LDL apheresis regimen. This pattern would not have been possible for most of the patients in the present study.

Compared with the period before LDL apheresis, HDL cholesterol increased by a mean of 25.0%, which further improved the LDL/HDL cholesterol ratio. As shown before, this increase is due to an increase in HDL_3 cholesterol,[9] which could be explained by the increased catabolism of very–low-density lipoprotein under therapy. A further possible beneficial effect of all three procedures applied is a long-term reduction of Lp(a) by 58.9%. Thus, in these patients with hereditary forms of hypercholesterolemia not adequately responding to diet and drug therapy, regular LDL apheresis produced a favorable lipid profile.

The results of the long-term follow-up study of coronary angiographies suggest that with the lipoprotein concentrations achieved, the progression of coronary heart disease can be stopped for a period as long as 8.6 years. The two patients presenting coronary lesions in bypass vessels had, on average, higher mean interval LDL cholesterol levles, but their native coronary lesions remained stable. This suggests that particularly following bypass surgery, it is essential to maintain LDL cholesterol levels at the most favorable concentration of less than 2.6 mmol/L.[4,6-8] In summary, all studies cited report a regression of coronary lesions in some and a halt in progression in most of the patients for periods of 2 years[16-19] and 3 years.[20] Our results demonstrate that in patients with FH not amenable to drug treatment, LDL apheresis and hypolipidemic drug treatment can stabilize coronary atherosclerotic lesions for periods up to 8.6 years.

In addition to the angiographically proven stabilization of coronary lesions, we also noted a considerable clinical improvement in our patients. Apart from three sudden deaths, for all of which an exact diagnosis could not be obtained, one nonfatal myocardial infarction, and five hospital admissions for unstable angina, there were no major coronary events. Moreover, there was an increase in daily exercise tolerance and a reduction in the frequency of angina in 21.7% of patients eligible for the coronary symptom score during LDL apheresis. This phenomenon has also been observed by others[16,19] and indicates that there must be early functional changes beyond angiographically detectable changes of coronary stenoses. More recent data indicate that a decrease in LDL cholesterol may positively affect a decrease in the vasomotor tonus of coronary stenoses stimu-

lated with acetylcholine.[21] This mechanism may be responsible for the improvement in exercise tolerance seen in these patients shortly after commencing LDL apheresis, which is in contrast to the results on coronary angiography.

In conclusion, aggressive reduction of LDL cholesterol with combined regular LDL apheresis (with any technique) and lipid-lowering drugs in patients with hereditary forms of hypercholesterolemia not adequately responding to drug therapy can prevent a progression of coronary artery disease in most cases. This stabilization of coronary lesions can be maintained for periods as long as 8.6 years. In four of 23 cases, an angiographically controlled regression of coronary atherosclerosis was achieved. The clinical improvement of coronary heart disease found in most patients suggests there may be functional changes that positively influence coronary blood flow despite an absence of change in angiographic findings. Yet it should be emphasized that this was not a controlled trial. Due to ethical reasons, it was not possible to include a control group. Therefore, we cannot prove by an experimental design that LDL apheresis is superior to other less effective LDL cholesterol-lowering methods. But the data show that in severe hypercholesterolemia, a cessation in the progression of coronary lesions can be obtained, which is, from a clinical point of view, a success.

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