European Journal of Clinical Investigation (1994) **24**, 724–732

The HELP-LDL-apheresis multicentre study, an angiographically assessed trial on the role of LDL-apheresis in the secondary prevention of coronary heart disease. II. Final evaluation of the effect of regular treatment on LDL-cholesterol plasma concentrations and the course of coronary heart disease*

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Received 19 July 1993 and in revised form 25 April 1994; accepted 3 May 1994

Abstract. The efficacy of the heparin-induced extracorporeal LDL-precipitation (HELP)-apheresis procedure has been studied in an open prospective multicentre trial. After 2 years of regular weekly HELP-treatment the data from 39 of 51 patients could be evaluated according to the study criteria. Twelve of the initially recruited study patients were omitted from the evaluation either because of premature termination of the treatment or because they did not fulfil the exact guidelines of the study protocol. A mean of 2·83 l plasma was regularly treated on average every 7·85 days. The mean pre-/post-apheresis LDL-cholesterol levels decreased from 286/121 mg dl^{-1} at the first HELP treatment to 203/77 mg dl^{-1} after 1 year and to 205/77 mg dl^{-1} after 2 years of regular apheresis; the corresponding values for fibrinogen were 314/144, 246/98 and 250/105 mg dl^{-1}, respectively. In contrast, the mean pre-/post-apheresis HDL-cholesterol levels rose from 41/38 through 51/44 mg dl^{-1} after 1 year to 52/43 mg dl^{-1} after 2 years of treatment. The overall result was a normalization of the atherogenic index (LDL-/HDL-cholesterol ratio) from 6·9/3·2 to 4·0/1·9. The angiographies from 33 patients obtained before and after 2 years of regular treatment could be evaluated blindly using the cardiovascular angiography analysis system. The mean degree of stenosis of all segments decreased from 32·5% (SD = 16) to 30·6% (SD = 16·8) over the 2 years. A regression > 8% was observed in 50/187 (26·7%) segments, whereas 29/187 (15·5%) segments showed progression. In 108/187 (57·8%) segments the lesions were stable (< 8% deviation) over 2 years. We conclude that regular treatment with HELP-LDL-apheresis is able to stabilize progressive atherosclerotic disease and to induce almost twice as much regression as progression of atherosclerotic lesions.

Keywords: coronary angiography, coronary heart disease, HDL-cholesterol, LDL-apheresis, LDL-cholesterol, regression of atherosclerosis.

Introduction

A large body of evidence links plasma cholesterol concentrations in a dose–dependent manner to an increased risk for coronary heart disease [1–3].

Recent studies have shown that effective lowering of LDL-cholesterol, particularly when paralleled by an increase in levels of HDL-cholesterol, leads to either retardation of the rate of progression or even to regression of coronary lesions as assessed by standardized coronary angiography [4,5]. Effective LDL-lowering by invasive means is also accompanied by a decrease in cardiac events and reduced total mortality, as recently shown in patients who underwent a partial ileal bypass [6].

Apart from invasive therapeutic strategies such as liver transplantation [7], ileum bypass operation [8,9] or portocaval shunt [10], the only effective therapy in patients with severe hypercholesterolaemia refractory to lipid lowering drugs is at present the regular

* Presented at the 26th Annual Scientific Meeting of the European Society for Clinical Investigation.

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extracorporeal elimination of LDL-cholesterol either by immunoadsorption [11,12], polyanion adsorption [13,14] or polyanion precipitation [15,16]. The latter procedure is based on the non-cationic co-precipitation at low pH and was therefore named 'Heparin-induced extracorporeal LDL-precipitation (HELP)' [17,18]. We now present a final evaluation of our 2 year multicentre study, conducted to prove the efficacy and safety of regular long-term treatment with the HELP-system as well as its clinical utility in secondary prevention of atherosclerosis and coronary artery disease (CAD) in patients with severe hypercholesterolaemia.

Methods

Study design

The details of the study design have been published [19]. Briefly, 51 patients with angiographically documented coronary artery disease (CAD) and severe hypercholesterolaemia (LDL-cholesterol $\geqslant 200\,mg\,dl^{-1}$ despite conventional diet and drug therapy) were recruited into the study in the 10 participating centres. At the initiation of this study, CSE-inhibiting drugs were not approved for regular use in Germany and were, therefore, not available for our patients.

Patients were only included if coronary artery bypass surgery or percutaneous transluminal coronary angioplasty (PTCA) were not treatment options or if bypass surgery had been performed in the past and reoperation was not considered because of diffuse atherosclerotic lesions in the peripheral coronary vessels.

Exclusion criteria were haemorrhagic diathesis, neoplasm, liver disease, severe cardiac insufficiency, cardiac valvular disease, apoplexy, dementia, non-compliance with dietary and drug therapy, or a break in regular treatment of more than 6 weeks.

All patients were made aware that this type of treatment was of unknown benefit with respect to progression of coronary artery disease, and before inclusion into the study the patients signed an informed consent. The study was approved by the local ethics committee of the University of Goettingen.

HELP-LDL-apheresis

The procedure of heparin-induced extracorporeal LDL-apheresis has been described in detail elsewhere [15,16]. Briefly, plasma and blood cells are separated by a $0{\cdot}55\,\mu m$ plasma filter. The plasma is then continuously mixed with a sodium acetate buffer (pH 4·85) containing $100\,U\,ml^{-1}$ heparin. The resulting precipitates are removed by filtration through a $0{\cdot}45\,\mu m$ polycarbonate filter and the excess heparin in the filtrate is adsorbed by a DEAE-cellulose filter. Finally, physiologic pH is restored and excess fluid removed by bicarbonate dialysis/ultrafiltration before the treated plasma is mixed with the blood cells from the plasma filter and returned to the patient.

All centres were equipped with a Plasmat™ Secura (B. Braun Melsungen, Melsungen, Germany) and were regularly supplied with the necessary sterile disposable filters and tubing systems required. Centres were required to treat 31 of the patients' plasma every 7 days with the exception of holidays and illness. Patients who for any reason had to interrupt treatment for an interval of 6 weeks or more were excluded from the final evaluation.

Coronary angiography

Detailed guidelines for standardization of the coronary angiography were included in the study protocol: the first and the second coronary angiogram, before and after 2 years of regular HELP-treatment at weekly intervals, had to be performed in identical projections with the angulation table and tube position being monitored at the first angiogram and reproduced at the second angiogram. Angiographic examination was performed after administration of 0·8 mg of nitroglycerine and 5 mg of isosorbid dinitrate.

Randomization and quantitative evaluation of angiographic films

Both the first and second angiograms of each patient were labelled 'A' or 'B' according to a computer-generated random list. The patient's identification, the name of the institution and the data of the investigation on the initial portion of the film were then concealed by a person not involved in the study. The randomized angiograms were evaluated side by side on two AX 35 cinefilm projectors; a zero reference frame was used to identify each individual frame of the film.

Identical projections of the major coronary arteries were selected for comparison and the respective frames were selected for quantitative angiography. If possible, diastolic frames were used. According to the selected frames a quantitative analysis of corresponding segments was performed by a medical technician using the cardiovascular angiography analysis system (CAAS) [20]. Each coronary segment was evaluated only once to avoid bias toward over-representation of segments with progression or regression which were evaluated in more than one projection. The projection with the highest degree of stenosis was used for evaluation. The results of the quantitative analysis of the blinded films were checked for comparability and plausibility by one of the investigators.

Segments were only included in the final analysis if they were fully opacified and visualized in identical projections in both films. The decision on inclusion or exclusion of an individual segment was based on the printout of the analysis of the isolated segments from the blinded films. The quality of the visualization (not a change of lumen or stenosis diameter) was the criterion for inclusion. Only close to perfectly matched segments were included in the analysis.

Table 1. Initial clinical and laboratory data of the patients recruited to the study and those under final evaluation after 24 months

Patients	*n*	M/F	Mi	ACVB	Smoker*	Hypertension	Age [years]	TC [mg dl^{-1}]	TG [mg dl^{-1}]	LDL-C [mg dl^{-1}]	HDL-C [mg dl^{-1}]	Fibrinogen [mg dl^{-1}]
All patients recruited	51	34/17	28	22	36	17	44·4 (9·2)	385 (94)	160 (89)	310 (86)	44 (13·9)	320 (98)
Patients evaluated after 2 years of regular apheresis	39	27/12	21	19	27	13	45·5 (7·9)	377 (84)	161 (94)	305 (84)	44 (14·4)	312 (95)
Patients evaluated by quantitative coronary angiography	33	23/10	16	14	21	11	47·2 (9·0)	365 (63)	(155) (97)	294 (14)	44 (89·1)	294 (82)

*Prior to diagnosis of CHD. Mi, myocardial infarction; ACVB, arteriocoronary venous bypass; TC, total cholesterol; TG, triglycerides.

Not all films analysed were suitable for comparative quantitative analysis: proximally occluded vessels with opacification via collaterals or via competitive flow could not be evaluated by quantitative analysis. Non-identical projections, different levels of inspiration, or the small size of diffusely diseased vessels were reasons for exclusion.

Grafts were not included in the analysis because many grafts were already occluded at the initial angiogram. Some of the grafts were too large for analysis by CAAS. In patients after bypass surgery, segments proximal to an anastomosis were only included in the analysis if there was no competitive flow in this segment.

The quantitative coronary analysis was performed using diameter stenosis of the segments. An increase or decrease in the diameter stenosis of 8% or more was considered to indicate regression or progression, respectively. Stenosis > 90% could not be evaluated because of methodological limitation.

Laboratory parameters

Total cholesterol, HDL-cholesterol and triglycerides were determined with commercially available test kits (Boehringer, Mannheim, Germany). LDL-cholesterol was measured using the Quantolip LDL test kit (Immuno, Heidelberg, Germany). The haematological, haemostaseological and clinical chemical parameters were determined in the respective laboratories of each centre.

Statistics

The data were statistically evaluated using exploratory data analysis. A global change over the period of 0, 12 and 24 months was tested using the Friedman Rank Test at a significance level of 5%.

Significant results were further subjected to the Wilcoxon sign-rank test to investigate differences between two timepoints (e.g. 0 and 12 months). The significance levels were adjusted by a modified Holm procedure as described by Shaffer [21]. Comparing changes in degree of stenosis as quantified by standardized coronary angiography, there was neither normal distribution nor symmetry, therefore the sign test was used as the most relevant method.

Results

Patient data

A total of 51 patients with severe coronary heart disease (CHD) and severe type II hyperlipoproteinaemia were recruited into the study (Table 1).

The patients' history of CHD, their risk profile and previous lipid lowering drugs which were maintained during HELP-treatment have been described in the first study report [19]. Forty-five patients completed 2 years of regular treatment while six patients were lost during the study (Table 2). As described in our previous paper two patients (patients 33 and 42) suffered non-treatment-related cardiac deaths during the first year of the study. Patient 25 suffered a fatal myocardial infarction (MI) at the beginning of the second year of the study that was also not related to the treatment procedure. The autopsy revealed a thrombotic stenosis of the right coronary artery. Patient 30 was lost to the study because of recurrent occlusion of his shunt, necessary for the treatment because of poor venous access. Patient 6 was lost to follow-up when she returned to her native country before completing the study. On the basis of the study guidelines, six patients in whom regular apheresis treatment was interrupted for a period of more than 6 weeks for several different reasons were classified as drop-outs and evaluated separately.

Technical details

For those patients ($n = 29$) who finished 2 years of regular treatment, the average treatment frequency interval was 7·85 days (SD = 4·15), each patient being treated on average 93 (SD = 10·0) times. Six patients

Table 2. Clinical and laboratory data of patients lost to follow up in 2 years of regular HELP-LDL-apheresis. Patients 13, 14, 15, 23, 24 and 51 interrupted regular treatment for > 6 weeks

Patient no.	M/F	Age [years]	LDL-C [mg dl^{-1}]* Initial	Final	Previous MI	ACVB	Total number of apheresis	Reasons for termination
6	F	18	540	230	–	–	26	Returned to native country
13	F	67	252	224 (200)	+	+	72 (25 + 47)	> 6 weeks break in treatment
14	M	49	197	222 (178)	+	+	88 (17 + 71)	> 6 weeks break in treatment
15	F	38	252	172 (228)	+	+	91 (48 + 43)	> 6 weeks break in treatment
23	M	36	366	373 (316)	–	+	77 (61 + 16)	> 6 weeks break in treatment
24	M	38	206	152 (197)	–	–	68 (6 + 62)	> 6 weeks break in treatment
25	M	40	359	227	+	–	53	Fatal MI
30	F	47	337	245	+	–	7	Problems of vascular access
33	F	32	318	250	+	+	14	Fatal MI
42	M	49	230	232	+	–	49	Sudden cardiac death
47	M	42	256	213	–	–	66	Kidney transplantation
51	M	60	211	181 (189)	–	–	91 (53 + 38)	> 6 weeks break in treatment

LDL-concentration before break in treatment in parentheses; the total number of aphereses is split in number of treatments before and after break. * Pre-apheresis values. MI, myocardial infarction; ACVB, arteriocoronary venous bypass.

who interrupted their regular treatment for more than 6 weeks underwent between 68 and 91 aphereses during their 2 years of treatment (*see* Table 2). Actual treatment times not including initial preparation lasted 115·27 min (SD = 21·66) and on average 2·831 (SD = 0·52) of plasma were treated at each visit. More than 2·51 of plasma could be treated in 91·5% of aphereses and more than 2·01 in 96·6% of aphereses.

Adverse clinical effects

From a total of 4330 individual aphereses on 51 patients primarily recruited into our study, 125 cases of undesirable side-effects were reported in 30 patients and are listed in Table 3.

Adverse clinical reactions were reported in only 2·9% of the treatments and the reactions were generally of minor clinical relevance. No major life-threatening complications occurred during treatment. The three sudden cardiac deaths described above occurred during the treatment-free interval. Despite the fact that HELP also affects some other heparin-binding proteins, no deficiency of any plasma protein under investigation was observed even after 2 years of regular treatment. The small reduction in pre-apheresis total protein concentrations presumably reflects the drop in the specifically precipitated apo B and fibrinogen and a dilution effect of around 4% due to the infusion of small amounts of isotonic solution used for prefilling the extracorporeal system (Table 4).

Positive clinical benefits

During the course of therapy there was a general improvement in the angina symptoms of our patients. At the onset of HELP therapy 32 of 39 patients finally evaluated reported suffering from angina symptoms while seven were free of it. After 2 years of regular treatment 15 patients of the 39 were free of angina symptoms.

Quantitative coronary angiography

Quantitative analysis of the corresponding films from the first and second coronary angiography in which at least two segments were comparable could be performed in 33 patients, including five of the six patients who, despite an interruption in therapy ranging from 7–16 weeks, still completed 2 years of regular HELP-therapy with a total of $\geqslant 67$ treatments (Table 2). Eleven patients who completed 2 years of regular HELP-treatment had to be excluded from the quantitative analysis either because of a missing control angiography or because of inadequate quality of the first or second angiogram.

Table 3. Clinical side-effects reported from 4330 single treatments during 2 years of regular HELP-LDL-apheresis

Side-effects	Frequency absolute (relative %)	No. of patients affected
Angina pectoris	44 (1·23)	5
Vagal reaction	36 (1·00)	19
Hypotension	[12 (0·33)]	[8]
Bradycardia < 60 min^{-1} nausea	[24 (0·67)]	[11]
Eye burning	13 (0·36)	4
Arrhythmia	7 (0·2)	5
Haematoma	6 (0·17)	3
Shunt occlusion*	5 (0·14)	4
Collapse	3 (0·08)	3
Shivering	3 (0·08)	3
Hypertension	2 (0·06)	1
Dyspnoe	2 (0·06)	2
Vertigo	2 (0·06)	2
Oedema	1 (0·03)	1
Headaches	1 (0·03)	1
Total	125 (2·88)	30†

* Does not include the data of the patient who was lost to the study on account of repeated shunt occlusion. † Several patients reported more than one side-effect.

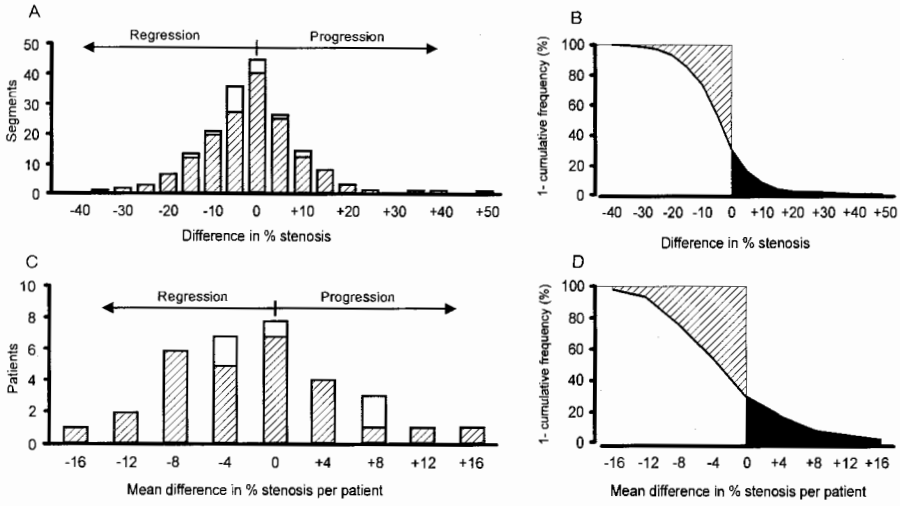

Figure 1. Angiographic changes in 187 segments from 33 patients under regular HELP-LDL-apheresis, including data from five patients (□) who, despite an interruption in therapy of 7–16 weeks, still completed 2 years of regular HELP-LDL-apheresis with at least 67 single treatments. (A) Distribution of the differences in the degree of stenoses evaluated for each segment before and after 2 years of HELP-LDL-apheresis ($S_{2yr}-S_{0yr}$; S = degree of stenosis in each segment; 0yr = before first treatment; 2yr = after 2 years of regular HELP-treatment). (B) Differences in stenosis shown as 1-cumulative frequency. ▨, the proportion of regression; ▩, the proportion of progression. (C) Distribution of the mean differences in stenosis based on the individual patient using the equation: $(S_{i2yr} - S_{i0yr})/n_i$. S_i = degree of stenosis in patient i; n_i = number of segments evaluated in patient i; 0yr = before first treatment; 2yr = after 2 years of regular HELP-treatment. (D) Mean differences in % stenosis per patient shown as 1-cumulative frequency. ▨, the proportion of regression; ▩, proportion of progression.

The analysis of a total of 187 coronary segments in 33 patients before (A) and after (B) 2 years of regular HELP treatment is summarized in Fig. 1 showing the distribution of the differences in per cent stenosis of the same segment. The positive values (stenosis B > stenosis A) indicate progression, whereas the negative values (stenosis B < stenosis A) represent regression. The distribution curve is shifted to the left, i.e. towards regression. This analysis was also performed on a patient basis. For each patient, the mean difference in per cent stenosis for all evaluated segments was calculated and presented as a distribution histogram (Fig. 1). Sixteen patients showed mainly regression (> 2% decrease of the mean stenosis) progression dominated in nine patients (> 2% increase of the mean stenosis), and in eight patients the coronary status did not change (Fig. 1). The mean degree of stenosis of all segments decreased from 32·5% (SD = 16·0) to 30·6% (SD = 16·8) ($P = 0{\cdot}0213$, assuming independence between segments); the mean degree of stenosis of all segments per patient decreased from 34·8% (SD = 10·8) to 33·3% (SD = 11·9) ($P = 0{\cdot}2153$).

To evaluate the effect of regular HELP-LDL-apheresis on stenoses of differing degree, the per cent stenosis of each segment was grouped into halves according to severity at the initial angiogram. Stenoses of ⩽30% ($n = 84$) did not change and stenoses > 30% ($n = 103$) showed a mean reduction of stenosis by 4·3% after 2 years of regular treatment ($P < 0{\cdot}001$). The mean cross-sectional area, therefore, increased by 16% in lesions showing initial stenoses of > 30% ($P = 0{\cdot}0001$). Using a difference in per cent stenosis of ⩾8% as a threshold for the evaluation of relevant changes in terms of regression or regression, 50 segment lesions (26·7%) regressed, whereas 108 segments (57·8%) did not change significantly. In 29 (15·5%) of the segments analysed, progression occurred.

Lipid lowering and angiographic results

Regular HELP-treatment at weekly intervals resulted in a significant long-term decrease of total cholesterol, LDL-cholesterol and triglycerides (Table 5), whereas HDL-cholesterol increased significantly. There was obviously no difference in the lipid lowering effect of LDL-cholesterol apheresis within the subgroup of patients undergoing re-angiography after 2 years, although the changes in the triglyceride concentrations were not on the same level of significance.

No correlation was found if changes in the coronary status (regression, no change, progression) were compared either to the extent of the lipid lowering or to changes of the LDL/HDL ratio. No correlation was observed between changes in the coronary status and the changes in the LDL/HDL ratio. There was also no detectable link between the absolute differences in LDL-C or HDL-C before and after each single treatment or the difference in lipoprotein concentrations before and after the regular treatment period and the degree of angiographic changes.

Table 4. The mean pre-apheresis values of clinical chemical, haematological and haemostaseological parameters before first treatment and after 1 and 2 years of regular HELP-LDL-apheresis

	Months of regular treatment					
	0		12		24	
Parameter	$n = 39$	$n = 33$	$n = 39$	$n = 33$	$n = 39$	$n = 33$
Sodium ($mmol\,l^{-1}$)	140·4 (2·8)	140·3 (2·7)	140·1 (3·2)	139·7 (3·0)	139·9 (2·4)	140·0 (2·3)
Potassium ($mmol\,l^{-1}$)	4·2 (0·3)	4·1 (0·3)	4·1 (0·4)	4·1 (0·3)	4·2 (0·3)	4·1 (0·3)
Calcium ($mmol\,l^{-1}$)	2·4 (0·12)	3·0 (0·2)	2·3 (0·1)	2·9 (0·2)	2·3 (0·1)	2·7 (0·2)
Total protein ($g\,l^{-1}$)	7·3 (0·7)	7·2 (0·8)	6·8 (0·5)	6·8 (0·4)	6·9 (0·5)	6·9 (0·6)
Albumin ($g\,l^{-1}$)	4·7 (0·7)	4·4 (0·4)	4·6 (0·9)	4·4 (0·4)	4·6 (0·8)	4·3 (0·5)
Complement C3 ($mg\,dl^{-1}$)	96 (30)	91 (23)	83 (25)	86 (23)	82 (18)	84 (14)
Complement C4 ($mg\,dl^{-1}$)	34 (13)	27 (11)	23 (8)	22 (8)	24 (5)	22 (6)
Haemoglobin ($g\,dl^{-1}$)	14·3 (1·7)	14·5 (1·8)	13·1 (2·0)	13·2 (2·0)	13·4 (1·8)	13·7 (1·7)
Haematocrit (%)	42·6 (5·4)	43·2 (5·5)	39·8 (6·2)	40·6 (6·4)	40·1 (4·8)	40·9 (9·8)
Erythrocytes ($T\,l^{-1}$)	4·7 (0·6)	4·8 (0·6)	4·5 (0·6)	4·6 (0·6)	4·5 (0·5)	4·6 (0·5)
Leucocytes ($G\,l^{-1}$)	6·7 (1·8)	6·3 (1·8)	5·6 (2·1)	6·1 (2·0)	6·7 (1·8)	6·2 (1·7)
Thrombocytes ($G\,l^{-1}$)	236 (60)	222 (54)	263 (70)	262 (66)	271 (78)	268 (70)
Fibrinogen ($mg\,dl^{-1}$)	328 (92)	287 (82)	252 (77)	235 (71)	254 (51)	246 (54)
Plasminogen ($mg\,dl^{-1}$)	11·3 (2·8)	9·2 (4·2)	12·6 (2·1)	9·3 (4·1)	11·7 (1·8)	9·0 (4·2)
Prothrombin time (%)	86·8 (21·2)	88·5 (18·1)	87·3 (20·2)	91·4 (9·5)	91·8 (17·2)	95·0 (8·8)
Partial thrombin time (s)	35·6 (15·5)	32·4 (7·9)	31·7 (8·0)	29·5 (5·1)	29·8 (7·9)	28·3 (3·6)
Thrombin time (s)	16·2 (2·0)	16·2 (2·1)	16·2 (6·2)	15·2 (4·0)	16·5 (5·7)	17·1 (7·7)

Mean out of 39 points; standard deviation in parentheses; right columns show the data of patients evaluated by quantitative angiography ($n = 33$, including five patients with break > 6 weeks).

Discussion

Plasma exchange and selective LDL-apheresis are effective treatment modalities for lowering plasma cholesterol levels in patients with severe type II hypercholesterolaemia [11,15,22].

The clinical utility of extracorporeal LDL-elimination was first demonstrated by Thompson *et al.* in suffering from homozygous familial hypercholesterolaemia (FH) children [23]. Regular plasma exchange therapy over a mean period of 8·6 years resulted in prolonged survival of the treated children as compared to their untreated siblings. After regular application of LDL-immunoadsorption over 2 years Hombach *et al.* [24] demonstrated regression of coronary atherosclerotic lesions by means of reangiography. Both studies, and a recent communication of Tatami *et al.* [25], prove unequivocally that extracorporeal LDL-cholesterol elimination is beneficial for patients with hypercholesterolaemia.

Our results clearly demonstrate that regular treatment with the heparin-induced extracorporeal LDL-precipitation favourably influences the course of progressive coronary artery disease. The natural history of coronary lesions in patients with severe hypercholesterolaemia is known from control groups of several prospective studies. Progression of coronary lesions occurs 3–7 times more frequently than regression within an observation period of 2–3 years [5,26,27]. In patients with only moderate lowering of plasma LDL-cholesterol concentrations, the incidence of progression is still higher than that of regression [26]. Recent studies have shown that a marked reduction of LDL-cholesterol and a parallel increase in HDL-cholesterol may lead to a higher incidence of regression than of progression [5]. In this context the LDL-/HDL-ratio seems to be of particular importance [28].

The results of the HELP-LDL-apheresis Multicentre Study are in agreement with the observations reported in the literature. In our patients with relatively high LDL-cholesterol values a reduction of the mean pre-apheresis LDL-cholesterol by −28·3%, an increase in the mean pre-apheresis HDL-cholesterol by +26·8%, and a consequent decrease in the mean atherogenic index (LDL-cholesterol/HDL-cholesterol) from 7·8 to 4·4 was accompanied by a twofold greater regression of coronary lesions than progression. We could not, however, find a statistically relevant correlation of the lipid-lowering effect and the angiographic outcome when tested on an individual basis.

The angiographic technique and the evaluation by quantitative coronary angiographies are of great importance for the interpretation of the results. Criticism may arise because only relative per cent diameter stenoses were evaluated. The relative parameter 'per cent diameter stenosis' was chosen due to the following reasons. A change of 8% or more of the relative percentage of stenosis was used as a threshold for progression or regression of disease between two consecutive films based on the medium- and long-term results of repeat studies by Reiber [29]. Upon commencement of the HELP-study, at the beginning of the quantitative coronary angiography era, the angiographic laboratories were not yet completely

Table 5. Serum lipid and lipoprotein concentrations before first treatment and after 1 and 2 years of regular HELP-LDL-apheresis

Parameter	All patients ($n = 39$) Months 0	12	24	Angiographically analysed ($n = 33$) patients Months 0	12	24
	***			***		
Total cholesterol [mg dl^{-1}]	***			***		
mean (SD)	361 (91)	279 (40)	281 (43) ($n = 38$)	341 (69)	271 (37)	278 (39)
S median	343	283	273	332	277	279
E mean (SD)	180 (58)	139 (23)	138 (22) ($n = 37$)	172 (48)	142 (23)	143 (22)
median	177	136	140	177	138	143
	*					
Triglyceride [mg dl^{-1}]	*					
S mean (SD)	187 (137)	149 (78)	145 (84)	190 (157)	159 (93)	153 (98)
mean	144	128	114	150·5	133	113
E mean (SD)	111 (110)	89 (69)	95 (63)	120 (135)	98 (74)	103 (75)
median	78	73	75	65	70	75
	***			***		
LDL-cholesterol [mg dl^{-1}]	***			***		
S mean (SD)	286 (88)	203 (40)	205 (43)	268 (67)	193 (35)	200 (38)
median	273	199	193	263	193	192
E mean (SD)	121 (55)	77 (24)	77 (20)	111 (46)	77 (23)	83 (20)
median	116	75	76	116	75	83
	**			**		
HDL-cholesterol [mg dl^{-1}]	**			**		
S mean (SD)	41 (10·8)	51 (11·7)	52 (12·9)	41 (11·6)	51 (13·6)	53 (14·8)
median	42	50	48	42	50	47
E mean (SD)	38 (14·8)	44 (11·0)	43 (11·6)	37 (12·8)	44 (12·1)	43 (12·9)
median	36	43	40	37	45	40

Mean out of 39 points; standard deviation in parentheses; right columns show the data of patients evaluated by quantitative angiography ($n = 33$, including five patients with break > 6 weeks). S = pre-apheresis concentrations; E = post-apheresis concentrations. * $P < 0{\cdot}05$; ** $P < 0{\cdot}01$; *** $P < 0.001$; significances were only tested for the pre-apheresis concentrations.

adapted for the quantitative evaluation procedure. Thus, the picture geometry could additionally vary, in spite of the effort taken on the exact reproduction of the different angulations. In some angiography laboratories the distance patient-image intensifier was not documentable and, in some cases, rather small catheters up to 5 french were used which, in the meantime, are known to be insufficient for exact calibration. All films were blinded with regard to institution and to time-sequence, therefore a systematic error favouring progression or regression can be excluded.

One of the major critical points of this study is the lack of a control group. Two arguments were decisive in not randomizing our patients to different treatment modalities. At the start of this trial HMG-CoA reductase inhibitors were only available for clinical trials and could not be included in our protocol, furthermore, our treatment procedure represented a last alternative in these patients, resistant to conventional therapeutic strategies, raising the ethical problem of restricting this therapy to randomly selected patients. This problem is still controversial and is relevant to other regression studies using lipid-lowering treatment.

A separate analysis of the lipid-lowering effect in those patients who were excluded from the quantitative evaluation of the angiograms illustrates that there is obviously no bias in selecting patients with preferentially outstanding lipid lowering for our regression analysis. The differences for the main lipid parameters, especially LDL- and HDL-cholesterol, but also the differences in fibrinogen, are not relevant. Although the very effective lowering of LDL-cholesterol, and probably also the increase in HDL-cholesterol, are the most likely reasons for the improvement of coronary findings, the small number of patients does not allow a conclusion on the final clinical outcome. The elimination of other plasma proteins of atherogenic potency such as Lp (a) and fibrinogen may have contributed to the favourable course of CHD in our patients. The effective decrease in plasma LDL-cholesterol may also induce changes in the coronary tone [30] or in the response of the coronary arteries to nitroglycerin, which was applied by the sublingual route before angiography. The

relative percentages of stenosis should be less affected by nitrates than the absolute values, nevertheless, a functional component may contribute to the increase of the cross-sectional area of all segments evaluated in our patients.

In contrast to conventional plasma exchange, HELP-LDL-apheresis is characterized by its selectivity. During each treatment LDL-cholesterol is removed with comparable efficacy; the HELP-procedure can, however, be applied more frequently thus leading to a much more efficient LDL-lowering over time without any major effect on other essential plasma proteins such as albumin, immunoglobulins and HDL. Therefore, changes in colloid-osmotic pressure with resulting oedema, increased susceptibility to infections and harmful effects on cholesterol metabolism are avoided.

Compared to plasmapheresis the HELP procedure is very safe, since no serious or lethal events have been reported during more than 4330 single treatments from this study. Acute treatment had to be interrupted in only three cases because of technical or medical problems such as haemolysis due to a handling error, clotting of the plasma filter and a severe vagal reaction in a patient not under ACE-inhibitor medication [31]. Adverse effects which were documented in 2·9% of all treatments could be managed without any major problem. The comparative overall rate of undesired adverse reactions of plasma exchange therapy is reported to be around 12% [32]. Three patients died during the interval between two treatments. One from sudden arrhythmia and consecutive ventricular fibrillation, a second from myocardial infarction after discontinuing anticoagulatory therapy with dicoumarol before tooth extraction, and the third patient died within the interval between two treatments after maximal exercise at home. In all three cases there was no apparent connection to the preceding HELP treatment.

Although therapeutic plasmapheresis can be considered as a safe procedure [33], Huestis [34] reported 60 lethal side-effects. They were predominantly attributable to the substitution of freshly frozen plasma which is not required in selective plasma therapy. Regarding the long-term safety of the HELP-procedure different laboratory parameters have been followed during 2 years of treatment and no deficiencies have been observed [35]. Therefore, the risk-benefit evaluation clearly demonstrates the superiority of HELP-apheresis over plasma-exchange therapy.

It might appear to be a shortcoming of the study that the basic drug treatment does not include HMG-CoA reductase inhibitors, which at the onset of the study were not regularly available in Germany. This circumstance allows us, however, to analyse the effect of HELP-apheresis, combined only with established drug treatment on the development of coronary stenoses. On the basis of our experience with regular HELP-LDL-apheresis we are hopeful that combined therapeutic modalities including HMG-CoA-reductase inhibitors will further favourably influence the long-term prognosis of patients suffering from severe hypercholesterolaemia and advanced CHD [36].

Acknowledgments

This work was supported by a grant (01 ZJ 8502) from the Bundesministerium für Forschung und Technologie.

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Appendix

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