LDL-Apheresis in the Treatment of Atherosclerotic Disease:

with focus on:

Heparin-mediated Extracorporeal LDL-Precipitation (H.E.L.P.)

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Fig. 1

Abstract

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Coronary artery disease still remains the leading cause of death in all industrialized countries.

It is now clear that a synergism of different mechanisms such as hypercholesterolemia, oxidative stress, diabetes mellitus, hypertension, genetic factors, life style and others play dominant roles. More recent knowledge provides evidence that chronic inflammation is also of key importance in the pathogenesis of cardiovascular disease and for clinical incidences of CHD. With the introduction of the statins it may be estimated that approximately 95% of all patients, who need therapy will achieve the recommended target concentrations of <100/70 mg/dl (NCEP ATP III guidelines) with adequate change in life style plus appropriate dietary and drug treatment. For a remaining small group of patients (<5 %) LDL-Apheresis has proven to be the most promising and safe method as an adjuvant therapy.

This is the clinical rationale for LDL-Apheresis.

Abstract (cont.)

Heparin-mediated Extracorporeal LDL-Precipitation (H.E.L.P.)

differs from all other techniques by relevant features:

- It allows concomitant drug treatment with ACE-inhibitors
- It reduces not only LDL and Lp(a) but also activated complement, fibrinogen, CRP, proinflammatory as well as procoagulatory factors with profound positive impact on hemostasiology and hemorheology.

The currently used H.E.L.P.-System provided by B. Braun Melsungen (BBM) has been well-accepted by the scientific and medical community for the past 20 years and has impressively proven its utility for the acute and chronic intervention of atherosclerosis-triggered clinical events.

LDL-Apheresis in the Treatment of Atherosclerotic Disease:

Heparin-mediated Extracorporeal LDL-Precipitation (H.E.L.P.)

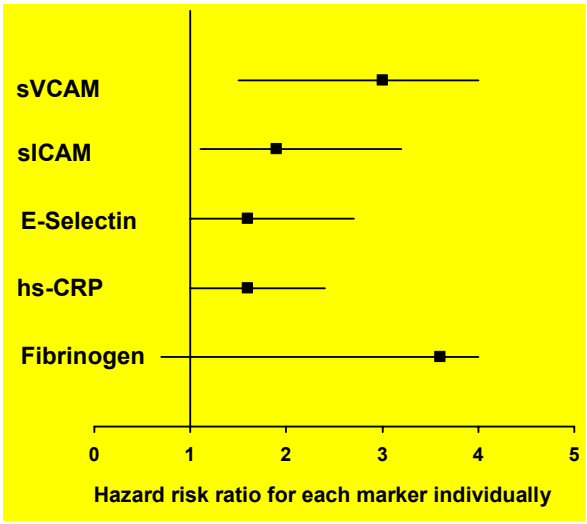
Coronary artery disease still remains the leading cause of death in all industrialized countries. In Germany, it claims an estimated 220000 lives of men and women and causes 200.000 non-lethal myocardial infarction (MI) events each year. Despite great efforts during in the last 30 years, still 25 % of men and 40 % of women die less than 12 months after their first myocardial infarction. The total (direct plus indirect) expenses for CHD in 2000 summed up to approximately 100 billion US $ in the US and to 57 billion € per year in Germany.

During the past decade, major improvements in our understanding of the mechanisms for the development of atherosclerotic lesions emerged. It appears that a synergism of different mechanisms including dyslipoproteinemia, primarily hypercholesterolemia with elevation of LDL-cholesterol, oxidative stress, diabetes mellitus, hypertension, genetic factors, life style and others play dominant roles. More recent knowledge provides evidence that chronic inflammation is also of key importance in the pathogenesis of cardiovascular disease and for clinical incidences of CHD (Fig. 2).

Along these lines of evidence, elevated LDL-cholesterol, Lp(a), inflammatory markers, Fibrinogen, CRP, IL-6 and various cytokines have clearly demonstrated power as predictors to identify people at risks for

future cardiovascular events. The same appears true for patients at risk for development oftransplant atherosclerosis and stroke.

Circulating Adhesion Molecules, CRP, Fibrinogen and Mortality in CHD Patients



Blankenberg et al., Circulation 2001

Fig. 2

This presentation will present facts on the therapeutic utility of LDL-apheresis with focus on

Heparin-mediated Extracorporeal LDL-Precipitation (H.E.L.P.)

to correct abnormal concentrations of LDL, Lp(a), inflammatory factors as well as of various cytokines leading to improvement of hemorheology and hemostasiology in patients suffering from atherosclerotic disease who are resistant to dietary and drug therapy alone.

Introduction:

Atherogenesis and Treatment Options today

Until the last 2 decades, management of coronary artery disease consisted mainly of a therapies designed to improve blood flow and oxygen supply to the heart, or to reduce myocardial oxygen consumption. Along this line angioplasty, bypass surgery and stenting of coronary arteries had become leading techniques, but only a minority (less than 50%) of patients at risk for CHD received a therapy to change the atherosclerotic process itself. This was true for most of our countries.

Atherosclerosis is a progressive disease characterized by the accumulation of lipids (cholesterol), fibrinogen, fibrous elements, calcium and by infiltration of various cell-types (T-lymphocyts, macrophages) as well as by proliferation of smooth muscle cells. Atherosclerotic plaques reflect an inflammatory mediated disease, driven by complex interactions between blood cells and cells of the vessel wall, resulting in the expression and release of cytokines, chemokines, vasoactive molecules, growth factors and proteolytic enzymes. Perpetuation of this cycle results in plaque rupture, thrombus formation and consequently clinical events (Fig. 3).

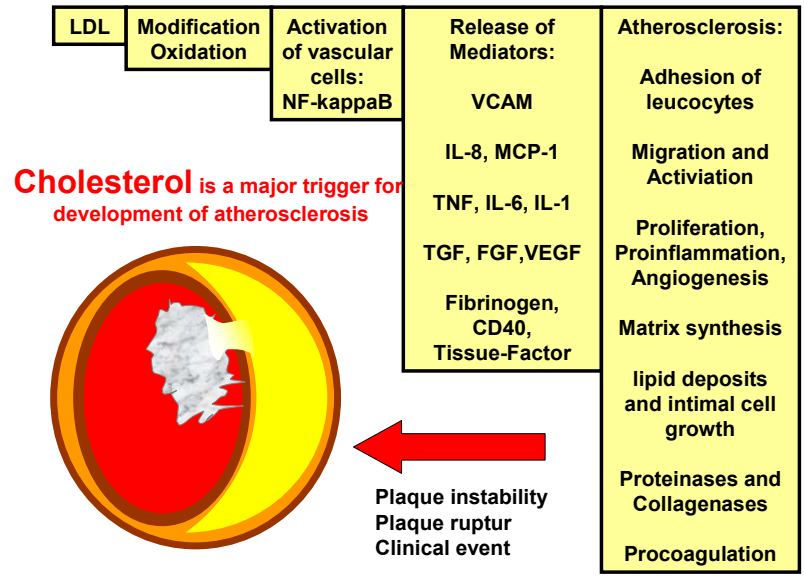


Fig. 3

Today very effective drug treatment measure Statins with or without cholesterol absorption blockers is available and has guided us toward appropriate treatment strategies for millions of patients. However, our understanding today based on vascular and molecular biology suggests that prophylaxis as well as therapy of CHD must address the entire atherosclerotic process (Fig. 4) and not just – although impressively effective – focus on invasive techniques to relieve coronary obstruction.

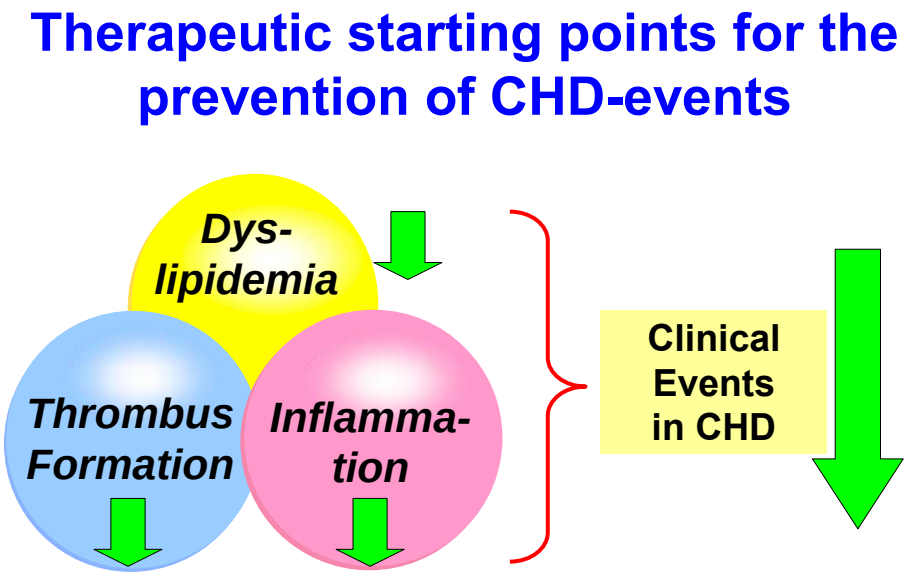


Fig. 4

It is now clear that therapies to lower cholesterol aggressively result in a significant decrease in cardiovascular events and mortality within one or two years after their start. This effect is long-lasting (Gotto AM, 1995)[1].

Since the introduction of the statins less than 2 decades ago more than 25 large primary and secondary prevention studies on more than 80000 randomized patients have substantiated the 4S results (Fig. 5) reported in 1994[2].

[1] Gotto AM. Lipid lowering, regression, and coronary events: a review of the Interdisciplinary Council in Lipids and Cardiovascular Risk Intervention, seventh council meeting. Circulation 1995; 92: 646-656

[2] Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: The Scandinavian Simvastatin Survival Study (4S). Lancet 1994; 344: 1383-1389

Secondary Prevention of CHD
* 4S-Study *

T.R. Pedersen et. al, The Lancet 19, 344, 1994

n = 4444 Pat., CHD and Tot. Chol. 210-310 mg/dl
randomised, double blinded; Simvastatin (20-40 mg/d : Placebo)
Duration: 5,4 years

Basic LDL x̄ 190 mg/dl ⟹ LDL - 35 % ; HDL + 8 %

Total Mortality	- 34 %
CHD Mortality	- 42 %
CHD Events	- 34 %
Revascularisation	- 37 %

Fig. 5

Relationship between the Prevalence of Cardio-vascular Events and Lowering LDL-Cholesterol

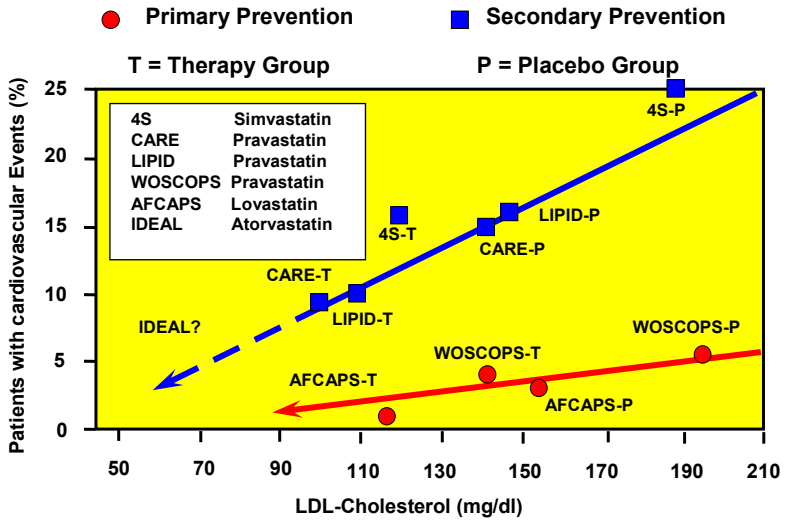


Fig. 6

30 mg/dl reduction of LDL-cholesterol will result in a 25% reduction of coronary events.

This effect is independent of starting concentrations of LDL-cholesterol.

The new NCEP ATP III guidelines, as well as the previous guidelines, recommend LDL cholesterol less than 100 mg/dl (now 70 mg/dl) as optimal for secondary prevention of CHD and for high risk subjects (Fig. 7).

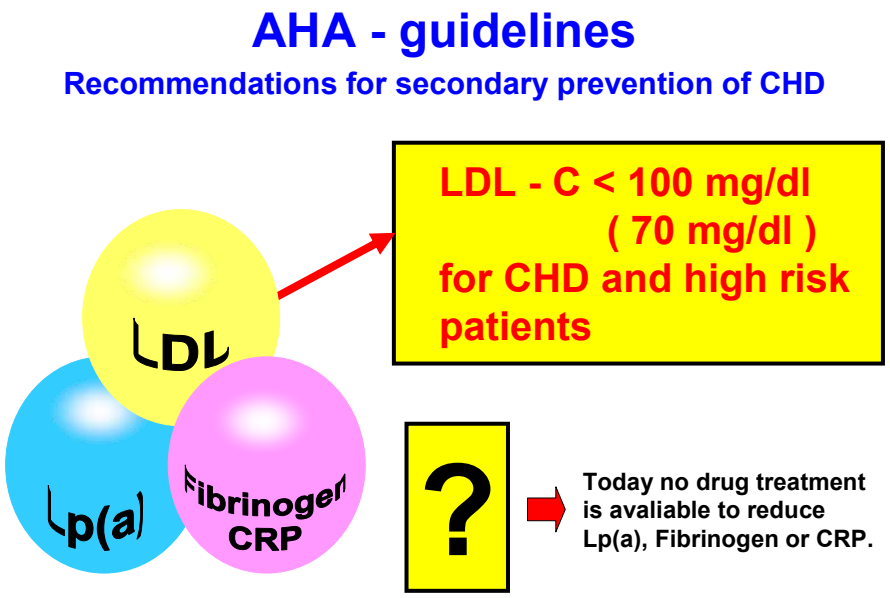


Fig. 7

It may be estimated that approximately 95% of all patients, who need therapy will achieve these target concentrations with an adequate change in lifestyle plus appropriate dietary and drug treatment. For the remaining small group of patients (<5 %), LDL-Apheresis has proven to be the most promising and safe method as an adjuvant therapy.

Rationale for LDL-Apheresis

It is the Individuum that Counts and not the Statistical Mean

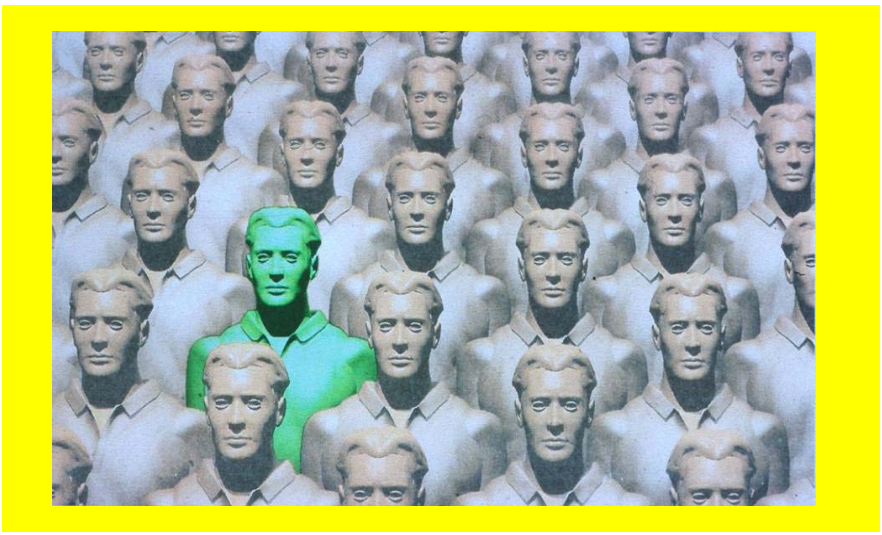


Fig. 8

Heparin-mediated Extracorporeal LDL-Precipitation (H.E.L.P.)

For patients resistant to dietary or drug treatment (low-density lipoproteins) LDL-Apheresis and plasma exchange have been used since the late 1970 (Lupien 1976[1], DeGennes 1976[2]) to quantitatively eliminate apolipoprotein B100 containing lipoproteins from the circulation of patients (Fig. 9).

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[1]Lupien PJ, Moojani S, Award J. A new approach to the management of familial hypercholesterolemia: removal of plasma cholesterol based on the principle of affinity chromatography. Lancet 1976; 1:1261-5

[2]DeGennes J-L, Touraine R, Maunand B, Truffert J et Laudat Ph.Formes homozygotes cutanéo-tendineuses de xanthomatose hypercholésterolémique dans une observation familiale exemplaire. Essai de plasmaphérèse à titre de traitement héroique. Société Médicale des Hôspiteaux de Paris 1976; 118:1377-1402

Cholesterol Metabolism in Humans and Approaches to lower Blood Cholesterol

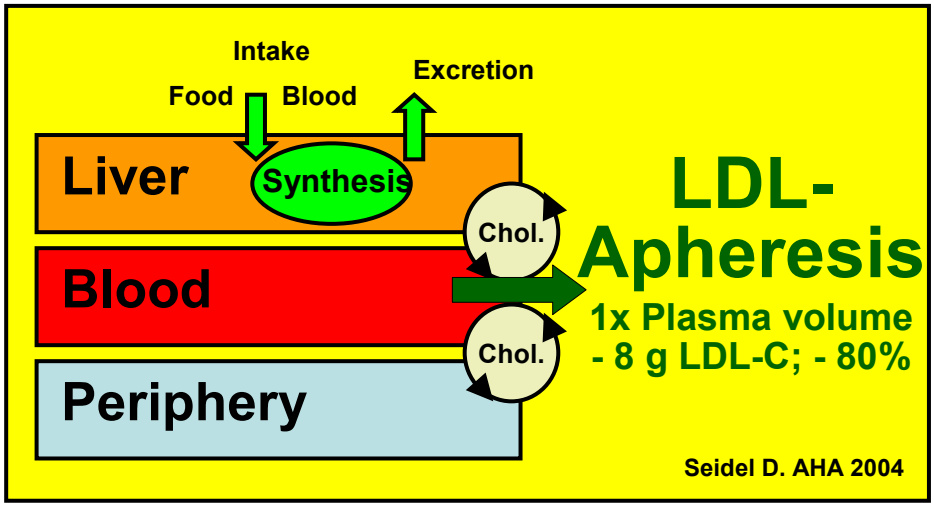


Fig. 9

Five different apheresis systems are available today.

LDL-Apheresis Techniques

- **Filtration** ***(Cascade, Thermo)***
- **Immuno-Adsorption**
  (Mono/Polyclonal Antibodies)
- **Dextran Sulfat Cellulose Adsorption** ***(DSC)***
- **Polyacrylate Adsorption** ***(DALI)***
- **Heparin Extracorporeal LDL/Fib Precipitation** ***(H.E.L.P.)***

Fig. 10

For all available systems effective removal of LDL and Lp(a) by a single apheresis procedure is well-documented in the literature. Only two, the H.E.L.P.- and the DSC-system, have worldwide approval, registration, and clinical distribution.

Adverse clinical events usually occur in less than 3% of patients. All extracorporeal LDL apheresis systems can be combined with a statin therapy, with such a combination resulting in a greater than 80% mean reduction of plasma LDL cholesterol. Negative charges on the surface of some materials used for adsorption such as DSC- and DALI do not allow concomitant treatment with angiotensin converting enzyme inhibitors, because of an excess increase of bradykinin activity.

The H.E.L.P. system does not carry this problem.

Heparin-mediated Extracorporeal LDL-Precipitation (H.E.L.P.)

The technique operates by an increase in the positive charges on LDL and Lp(a) particles at low pH (5.12), allowing them to specifically form a network with heparin and fibrinogen in the absence of divalent cations (Seidel D. and Wieland H., 1982[114], Wieland H. and Seidel D.1983[155]). As will be discussed further in this presentation, only a limited number of other heparin-binding plasma proteins are coprecipiated by heparin at low pH. Proteins such as apo A, albumin or immunoglobulins do not significantly bind to heparin at low pH and are not precipitated in the system (Eisenhauer et al., 1987[22]).

Complement activation takes place in all extracorporeal circuits. However, as a specific feature of the H.E.L.P.-system, the activated complement C3a, C4a as well as the terminal complement complex are highly adsorbed to the precipitation filter resulting in plasma concentrations actually below those measured before apheresis (Würzner 1991[158]).

Heparin-mediated Extracorporeal LDL-Precipitation (H.E.L.P.)

The H.E.L.P.-system works in 5 major steps to remove the atherogenic compounds from the blood. These steps are illustrated in the flow sheet (Fig. 11).

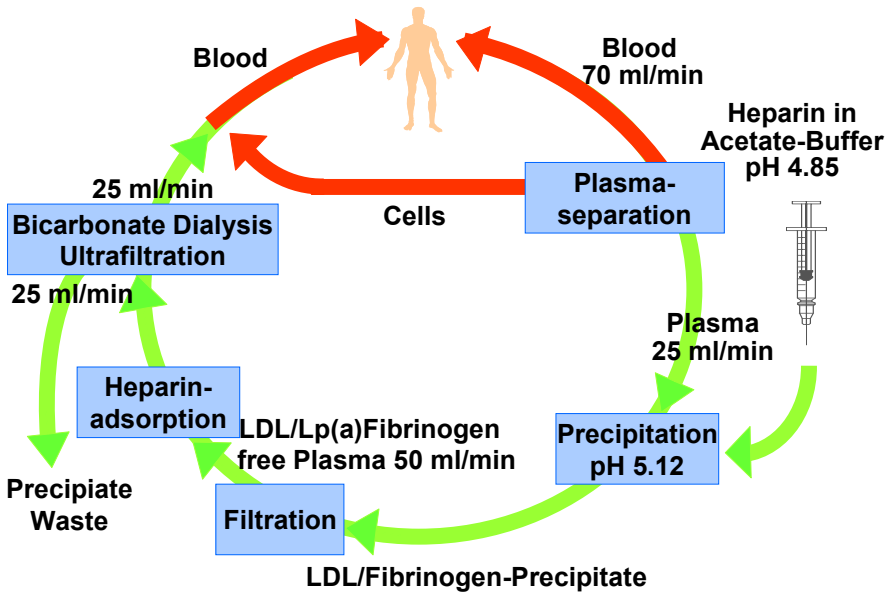


Fig. 11

In the first step, plasma is obtained by filtration of whole blood through a plasma separator. Plasma is then mixed continuously with a 0.3 M acetate buffer of pH 4.85 containing 100 IU heparin/ml. Sudden precipitation occurs at the final pH of 5.12. The suspension is circulated through a 0.4 µm polycarbonate filter to remove the precipitated LDL, Lp(a), inflammatory and procoagulatory factors.

Excess heparin is adsorbed by passage through an anion-exchange device. The plasma buffer mixture is finally subjected to a bicarbonate dialysis with ultrafiltration to remove excess fluid and to restore the physiological pH before the plasma is mixed with the blood cells and returned to the patient. All filters and tubings required for the treatment are sterile, disposable and are intended for single use only.

H.E.L.P.®-System by B. Braun Melsungen*

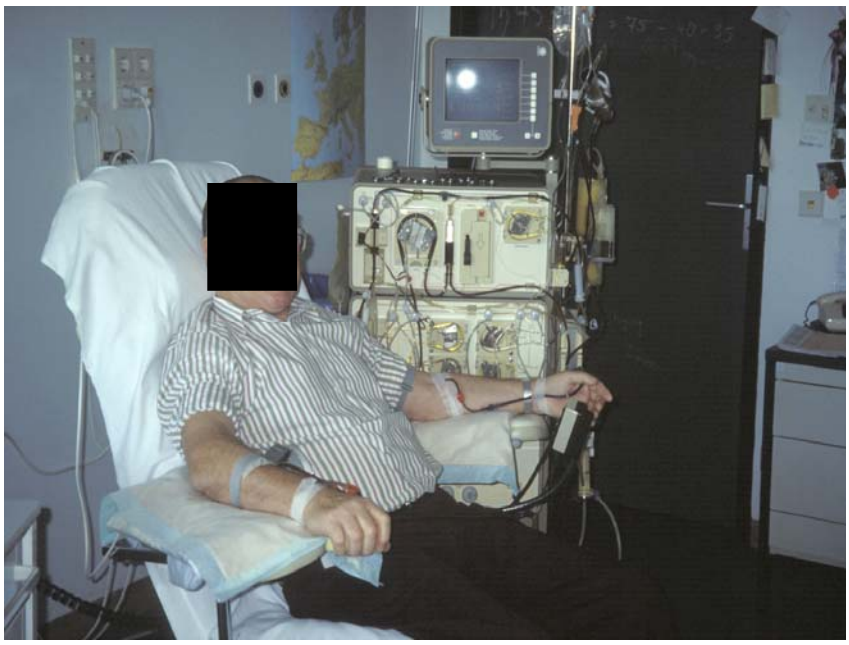


Fig. 12

Treatment of one volume of plasma takes approximately 2 hours.

* B. Braun Melsungen AG, Schwarzenberger Weg 53, 34212 Melsungen

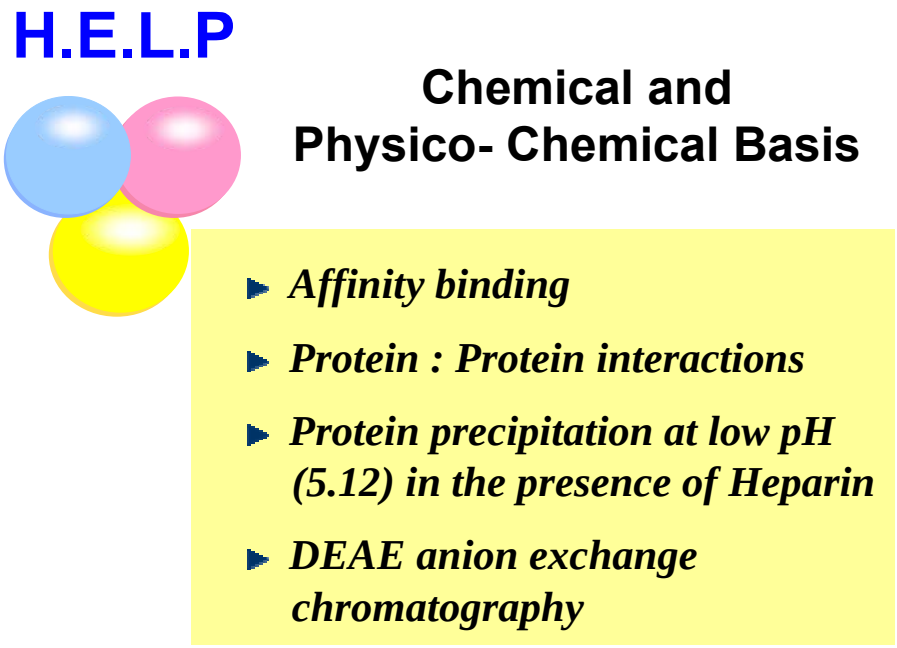


Fig. 13

Because of the specific but complex chemical-, biochemical- and physico chemical basis of the H.E.L.P. technique (Fig. 13) characterized by affinity binding, by Protein:Protein interactions and precipitation of blood compounds at low pH (5.12) in the presence of Heparin and DEAE anion-exchange chromatography, it has become apparent that the H.E.L.P. system differs from all other techniques with regard to its specificity.

The H.E.L.P.-system is unique in the way that it removes not only LDL and Lp(a), but also fibrinogen, CRP and many other potentially atherogenic factors with high efficacy (Fig. 14)

H.E.L.P. - Treatment

Long – term effects

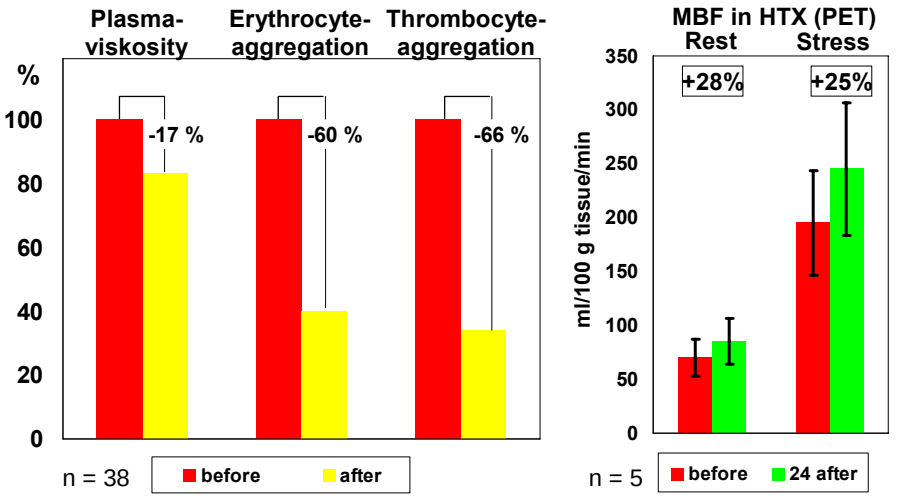
Mean interval values of app. 6000 treatments

LDL	- 51 %	±	14
Lp(a)	- 45 %	±	5
HDL	+ 12 %	±	3
Apo B	- 46 %	±	10
Apo A1	+ 9 %	±	2
Fibrinogen	- 46 %	±	15

Fig. 14

The reduction of both fibrinogen and LDL is of considerable impact on blood viscosity, platelet and erythrocyte aggregation (Fig. 15).

Influence of H.E.L.P. on Hemostasiology and Myocardial Blood Flow (PET)



Seidel D. Zeitschrift Kardiol, 92 6 2003

Jaeger et al. JHLT, 2004

Fig. 15

Changes in viscosity improve oxygen and thereby nutrient supply to tissues (+ 30%, Fig. 15 and 16). In addition chronic H.E.L.P.treatment modulates expression of genes with promoter elements responding to shear stress and vasomotion (see specific references).

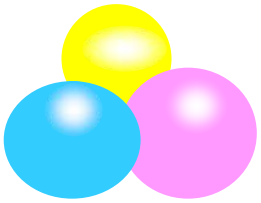
Improvement of Coronary Vasodilatation Capacity through H.E.L.P Therapy
(Positron Emission Tomography: PET)

Myocardial blood flow after Dipyridamole stress [ml/min per 100g]		Coronary flow reserve	Minimal Coronary Resistance [mm Hg/min/100g/ml]
Pre H.E.L.P	173 ± 63	1.9 ± 0.7	0.6 ± 0.7
Post H.E.L.P	226 ± 79	2.5 ± 0.7	2.5 ± 0.7
% Change	31	24	30
	p<0.01	p<0.02	p<0.01

Mellwig et al. Atherosclerosis 139:173-178, 1998

Fig. 16

Heparin-mediated Extracorporeal LDL-Precipitation (H.E.L.P.)



Clinical Experience
1984 - 2005

More than 250000 treatments world wide

More than 1200 patients

Some patients are treated for over 20 years

No safety concerns on acute or long term treatment

Full compatibility with drugs

Operating H.E.L.P. Centers in Europa, Asia, USA

Fig. 17

No doubt, the largest and best published controlled clinical studies demonstrating reduction of clinical events by LDL-Aapheresis were obtained with the H.E.L.P. system. (Fig. 18-26)

See comprehensive literature listed below for selected publications pertaining to the H.E.L.P.-System and the clinical utility of H.E.L.P.-treatment.

First Cinical Intervention Studies with H.E.L.P. in high risk Patients

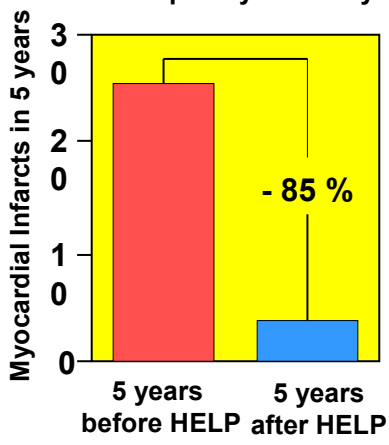
		Ref.:
Treatment of homozygous FH	**(1990)**	135,45
Plaque stabilization, regression	**(1994,1999)**	102,104
Reduction of coronary events	**(1998)**	137
Prevention and therapy of GVD	**(1996,1997)**	37,39
Improvement of endoth. function	**(1998)**	73
Improvement of hemorheology	**(1990)**	99

Comprehensive Bibliography is listed below

Fig. 18

Reduction of Myocardial Infarcts and Regression of CHD under long term H.E.L.P. Therapy

Myocardial infarcts (180 FH patients)
HELP-Frequency: 10.7 days



H.E.L.P.- Multicenter Study

Analysis of 187 Coronary Segments in 33 CHD Patients (2 years)

Regression 107 Seg.
Unchanged 5 Seg.
Progression 75 Seg.

Regr. / Prog.: 1.4

(Ref.:28,97,102,107,119,122,136,137,138)

Fig. 19

The H.E.L.P multicenter study:
an angiographically assessed trial

n = 51 HR-CHD

Follow up of 187 segments after 2 years of regular treatment

Mean reduction of all stenosis	**2.0 %**
Mean reduction of all all segments with stenosis >30 %	**4.3 %**
Mean increase of cross sectional area in segments with stenosis >30%	**16 %**

Ref.: 28,102,104

Fig. 20

Secondary Prevention of CVD: Risk Reduction under H.E.L.P. as compared to Drug Intervention

Treatment	Patients	Mean Duration (years)	Patient-years	Events / 1000 patient years	Reduction in %
I. Coronary Infarctions					
Drug only	186	5	930	28	
Drug + H.E.L.P.	186	5	930	4,3	85
4S Control	2223	5,4	12000	23	
4S Simvastatin	2221	5,4	12000	14	39
II. Total Mortality					
Drug + H.E.L.P.	829	5	4145	11,6	44
4S Control	2223	5,4	12000	21	100
4S Simvastatin	2221	5,4	12000	15	29

(for details see Ref.: 123)

Fig. 21

Clinical Reports of High Risk Patients: Individual Follow-ups

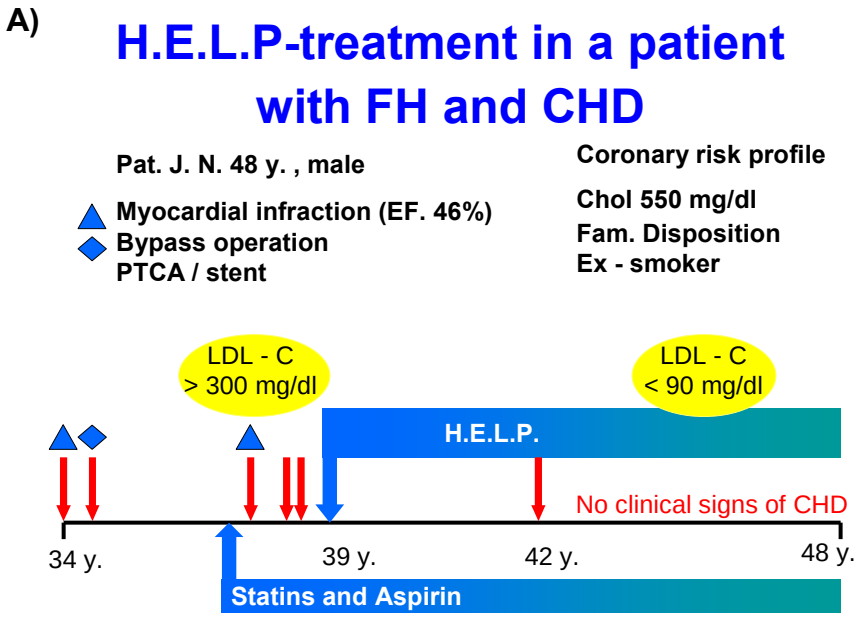


Fig. 22

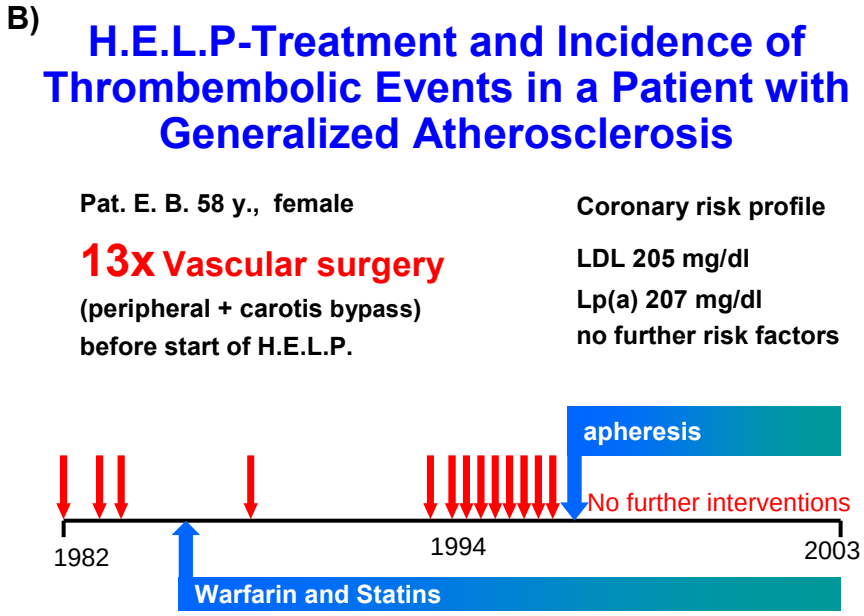
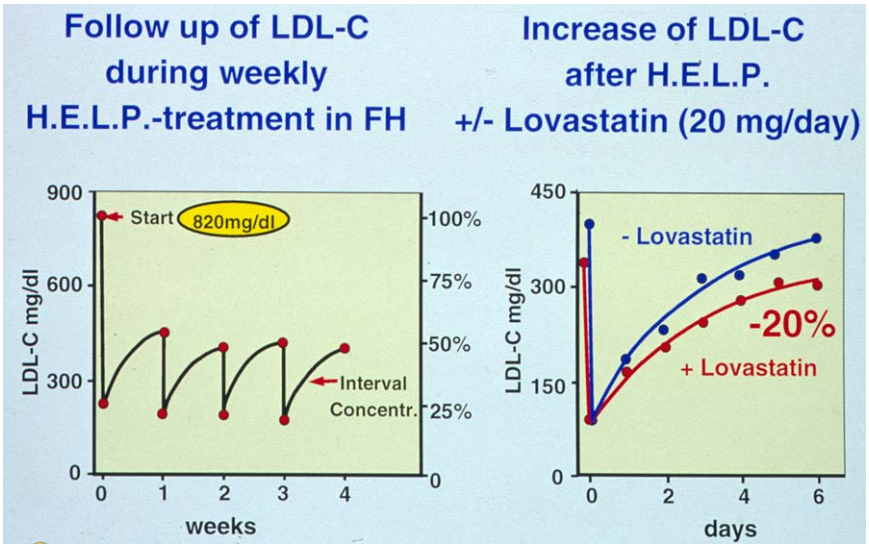


Fig. 23

Long-term Treatment of a Homozygous FH Girl.

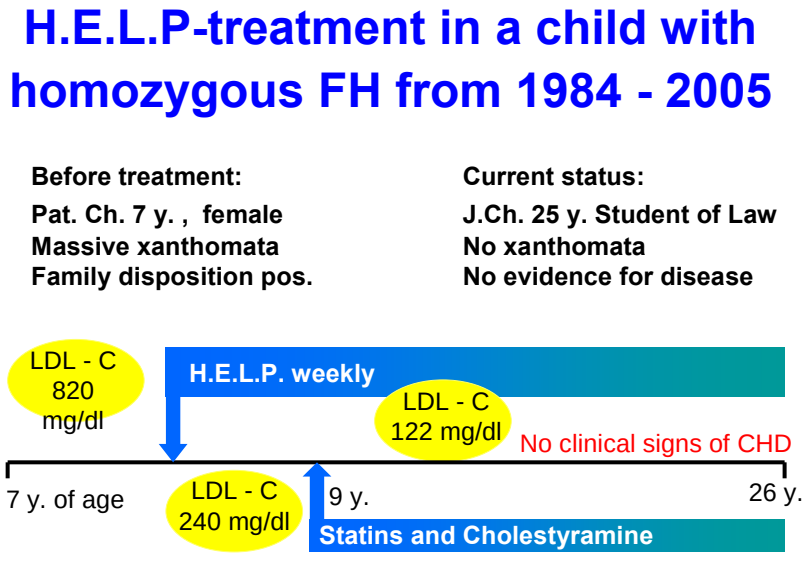
Treatment was started when the patient was 7 years old. Under regular (weekly) H.E.L.P.-treatment she developed well. No treatment complications ever took place; her coronary arteries are uneffected up until now (25 years old) (see Fig. 24-27).

(Thiery et al. 1990[135], Jaeger et al. 2002[45])



Thiery et al. 1990, 135

Fig. 24



LDL is expressed as mean-interval value between 2 treatments

Fig. 25

Regression of Atheroma under H.E.L.P. Therapy in a Homozygous FH patient

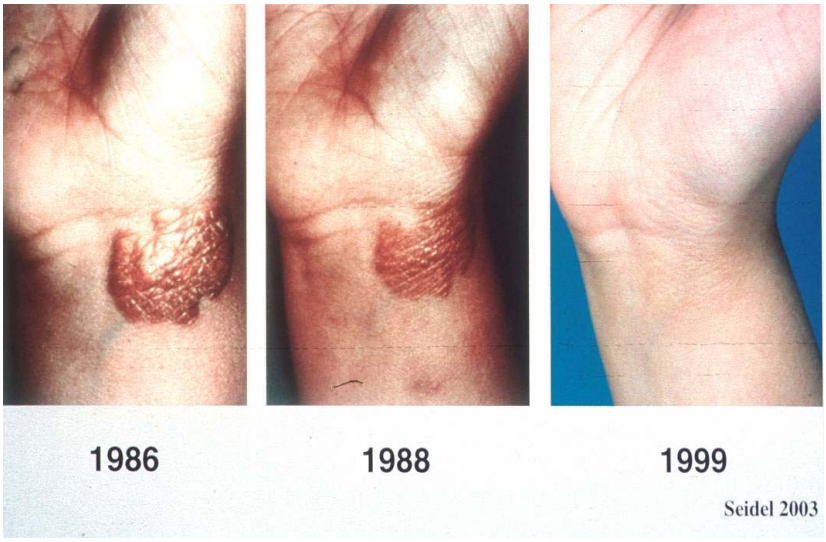


Fig. 26

Long-term (20 y) treatment with H.E.L.P.-Apheresis of a homozygous fam. hypercholesterolemia female

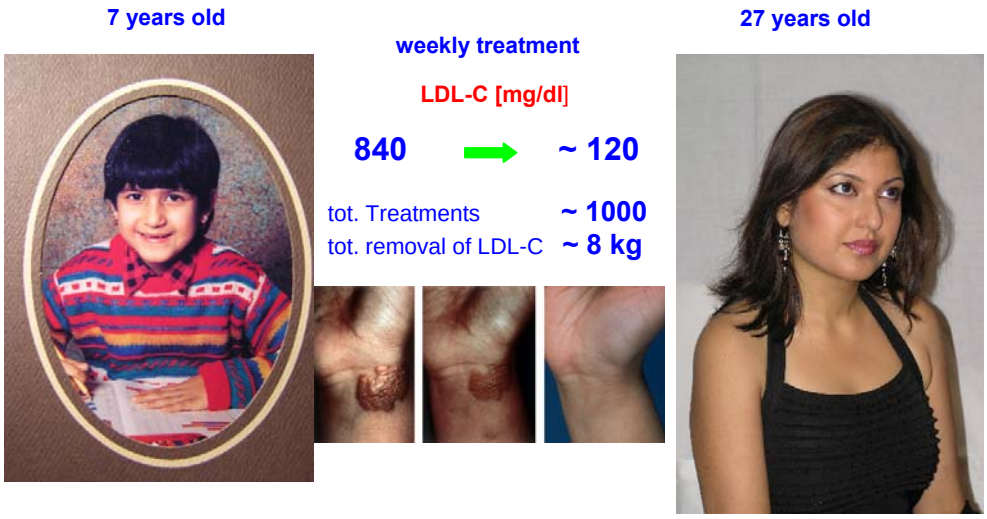


Fig. 27

No doubt LDL-Apheresis is the ultimate as well as most efficient treatment for patients suffering from the homozygous form of FH.

Heparin-mediated Extracorporeal LDL-Precipitation (H.E.L.P.)

Focus on the reduction of inflammatory and procoagulatory factors.

Because of the specific chemical and physicochemical basis of the H.E.L.P. technique characterized by affinity binding, Protein:Protein interaction, and protein precipitation at low pH (5.12) in the presence of Heparin and DEAE anion-exchange chromatography we became interested in monitoring the effect of H.E.L.P. treatment with particular focus on the modulation of coagulatory- and proinflammatory factors and markers.

As demonstrated here and in part previous publications H.E.L.P. therapy decreases major inflammatory factors to the order of 25-65%, most major inflammatory factors have been shown to be elevated in CHD and HTX patients (Fig. 28, 29).

Modulation of Circulating Proinflammatory Factors and Markers by a Single HELP Apheresis in CHD

in part taken from Wang et al. Atherosclerosis 2004

Parameter	% Difference Pre/Post	P-Value
LDL peroxidation (TBARS)*	- 21.0	<0.001
Homocystein	- 21.6	<0.001
MCP-1	- 15.0	<0.001
sVCAM-1	- 36	<0.001
sE-Selectin	- 23.6	<0.001
TNF-α	- 36.0	<0.001
TNF-α p75 Rec.	- 29.5	<0.001
hs-CRP	- 66.9	<0.001
Endothelin	- 49.0	<0.001
LBP	- 26.7	<0.001
Endotoxin**	- 49.0	<0.001

* Wieland et al. Eur J Clin Invest 1995, ** Samtleben et al. Artif Organs 1998

Fig. 28

Hemostatic Factors within Normal Range in CHD Patients: Changes by H.E.L.P. Therapy

(n = 18) Wang et al. unpublished

Parameter	before H.E.L.P.	after H.E.L.P.	Δ (%)
Prothrombin (%)	102 ± 16	46 ± 8	- 55
Factor V (%)	115 ± 19	50 ± 9	- 57
Plasminogen (%)	118 ± 19	59 ± 13	- 50
Factor X (%)	103 ± 31	88 ± 18	- 45
Factor XI (%)	117 ± 26	51 ± 13	- 56
Factor XIII (%)	114 ± 31	63 ± 19	- 45
Antithrombin	117 ± 21	88 ± 13	- 25
Protein S (%)	106 ± 9	69 ± 22	- 35
Protein C (%)	118 ± 27	59 ± 16	- 48

In part taken from Jaeger et al. 2001 (43)

Fig. 29

Increased Procoagulatory Factors in HTX or CHD Patients: Changes by H.E.L.P. Therapy

(n=18)

Parameter	before H.E.L.P.	after H.E.L.P.	Δ (%)
Fibrinogen (mg/dl)	413 ± 124 ↑	173 ± 71	- 58
Willebrand F. (%)	193 ± 78 ↑	85 ± 33	- 56
sCD40L* [ng/ml]	5.3 ± 2.6 ↑	3.8 ± 2.4	- 16
Tissue factor (pg/ml)	280 ± 118 ↑	211 ± 113	- 27
Factor VIII (%)	195 ± 48 ↑	83 ± 32	- 57
Factor IX (%)	160 ± 31 ↑	88 ± 18	- 45
Factor VII (%)	136 ± 43 ↑	92 ± 32	- 32

In part taken from Jaeger et al. 2001 (43)

Fig. 30

Since inflammation and thrombus formation are connected it is not unexpected that patients with ischemic heart disease or HTX develop hypercoagulability. Due to their heparin binding site important factors such as fibrinogen, von-Willebrand-Factor, sCD40L, Tissue Factor, Factor VII, VIII and IX are decreased by H.E.L.P. treatment by 30 up to 60%; see Fig. 30. Other hemeostatic factors including prothrombin and factor V are also decreased by H.E.L.P. treatment but remain within normal range as do the fibrinolytic factors plasminogen, factor X, XI and XIII, Antithrombin Proteins C and S; see Fig. 29.

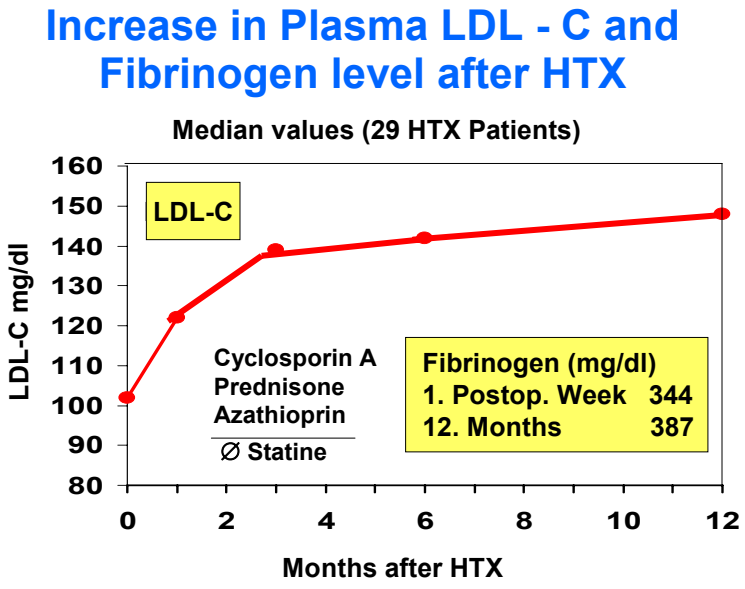
Unlike fibrinolytic therapies such as *t*-PA, H.E.L.P. apheresis provides a controlled reduction of clotting factors. APTT is not significantly prolonged Prothrombin time is decreased by 30 - 40 % but declines quickly within 1- to 2 h after the procedure.

No relevant bleeding problems have ever been reported for the H.E.L.P. treatment.

Heparin-mediated Extracorporeal LDL-Precipitation (H.E.L.P.)

in the Treatment of Cardiac Allograft Vasculopathy

Cardiac allograft vasculopathy reflects a stimulated inflammatory machinery and is often associated with hypercoagulability and increased concentrations of LDL-C (Fig. 31). We hypothesised that long lasting drastic reduction of LDL-C, Fibrinogen, CRP, procoagulatory factors and inflammation markers prolongs survival in heart transplanted patients suffering from graft atherosclerosis.



Blessing et al. , unpublished

Fig. 31

On the basis of this hypothesis we initiated a multicenter study following 28 HTX patients suffering from documented cardiac allograft vasculopathy (documented by IVUS) and hypercholesterolemia (LDL >185 mg/dl). 80% of the patients had elevated Fibrinogen and CRP concentrations at start. The objective of this study was to reduce all cause mortality by chronic H.E.L.P. treatment in comparison to conventional therapy (ISHLT multicenter analysis, register report 2000) (Fig. 32). The outcome expressed as prolongation of survival time clearly indicates that chronic H.E.L.P.Apheresis treatment reduces the mortality rate significantly by more than 60 %, for more than 10 years in such high risk patients, i.e. a doubling of the survival time as compared to standard therapy (Jaeger et al., 2002[46]).

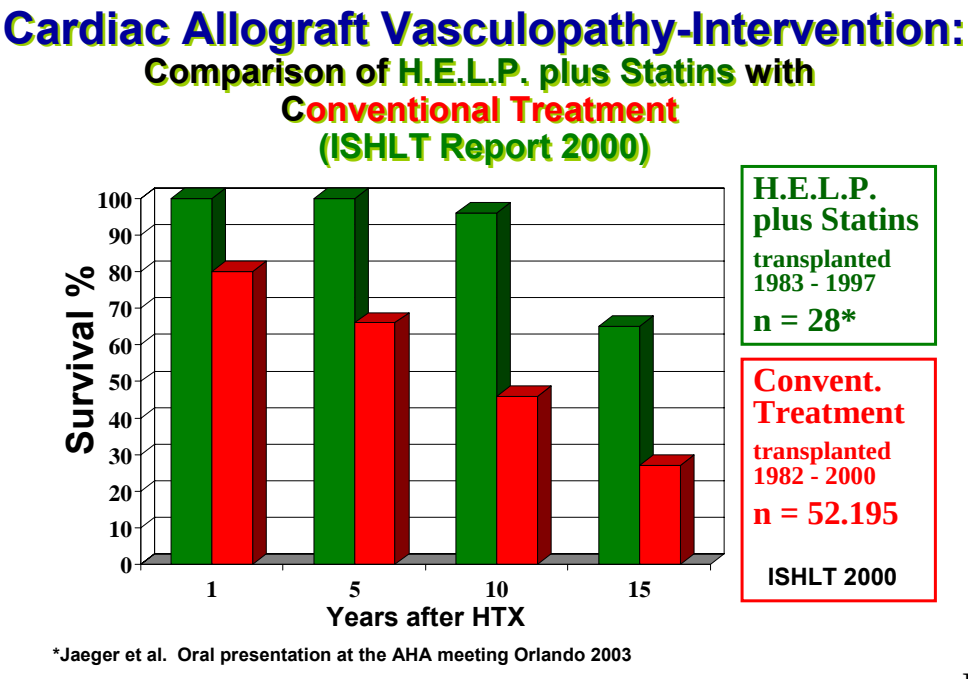


Fig. 32

The result of this important study is in agreement with an earlier report by Park et al. (1997[82]) (Fig. 33) who demonstrated regression of cardiac allograft vasculopathy in a case control study of 8 HTX patients followed for 38 month.

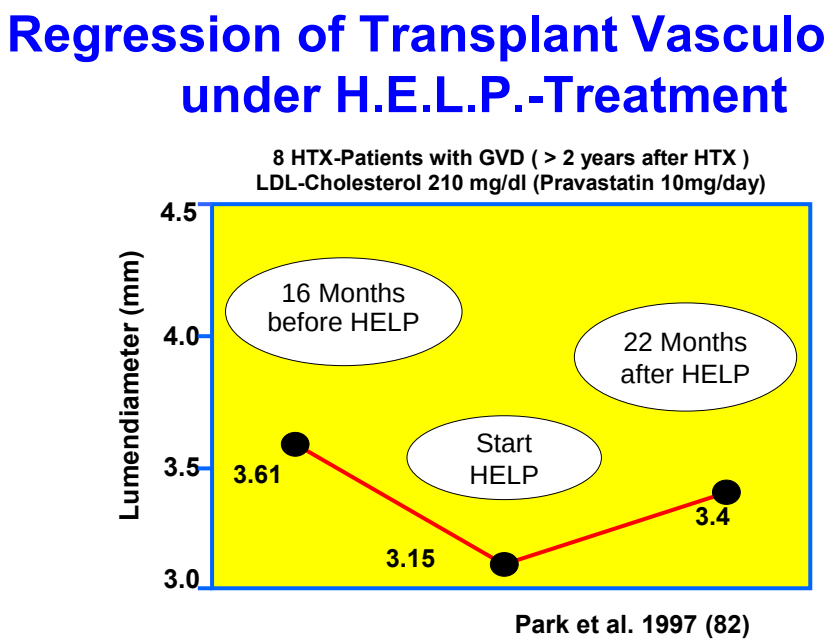


Fig. 33

There is also agreement with the outcome of a small intention-to-treat pilot study on 20 patients (10/10) suffering from hyperfibrinogenemia with or without elevated LDL. The intention of this study was to prevent graftvasculopathy after heart transplantation with chronic H.E.L.P. therapy (Jaeger et al. 1997 [36, 37]) see Fig. 34.

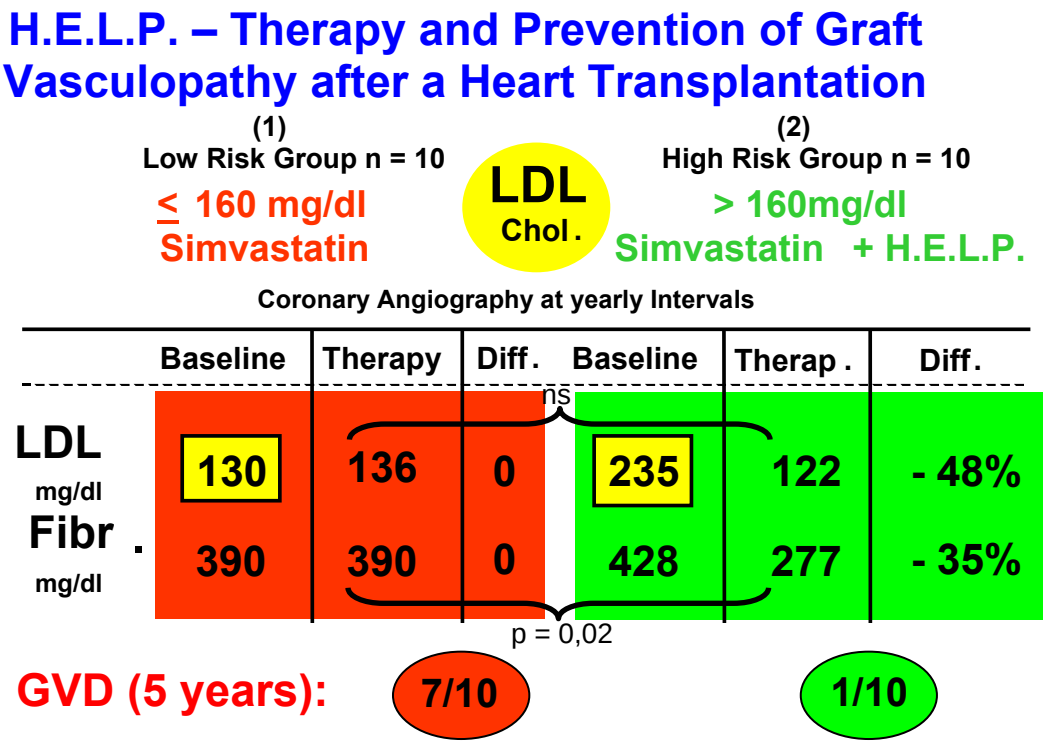


Fig. 34

The outcome of this study clearly indicates the benefit of chronic H.E.L.P. treatment after heart transplantation for the protection from graft vasculopathy.

In the low risk group (1, Simvastatin) with starting LDL concentrations <160 mg/dl, 7 out of 10 patients developed graft vasulopathy in the follow-up period of 5 years. In striking contrast in the high risk group (2; Simvastatin + H.E.L.P.) with starting LDL concentration >160 mg/dl only 1 out of 10 developed graft vasculopathy over 5 years.

Even with low-dose statin therapy (high doses are not well tolerated in transplanted patients) Graft Vasculo Disease (GVD) is the principle cause of organ failure and life-limitation for HTX patients.

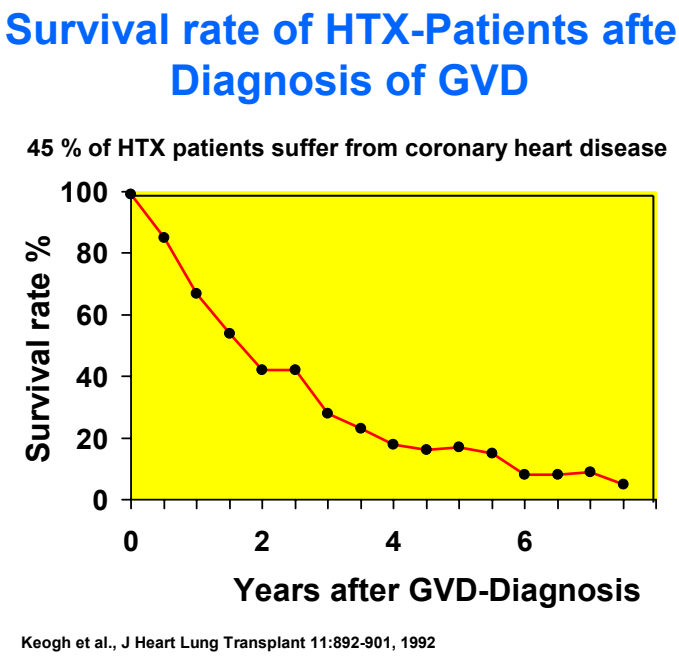


Fig. 35

Conclusion:

The data presented here are in agreement with our clinical experience with the H.E.L.P. therapy for almost 20 years.

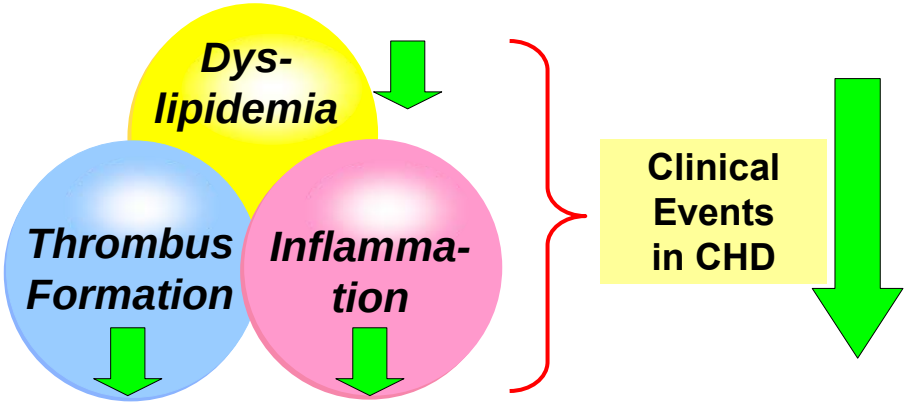


Fig. 36

Because lipid metabolism, inflammation and thrombus formation play key roles in the development of clinical events in atherosclerotic disease, a therapy to modulate the interaction of all three biological systems to normal seems logical (Fig. 36). An apheresis system which removes proatherogenic lipoproteins, proinflammatory- and procoagulatory factors simultaneously is recommended as the therapy of choice for high risks patients who are refractory to drug treatment alone.

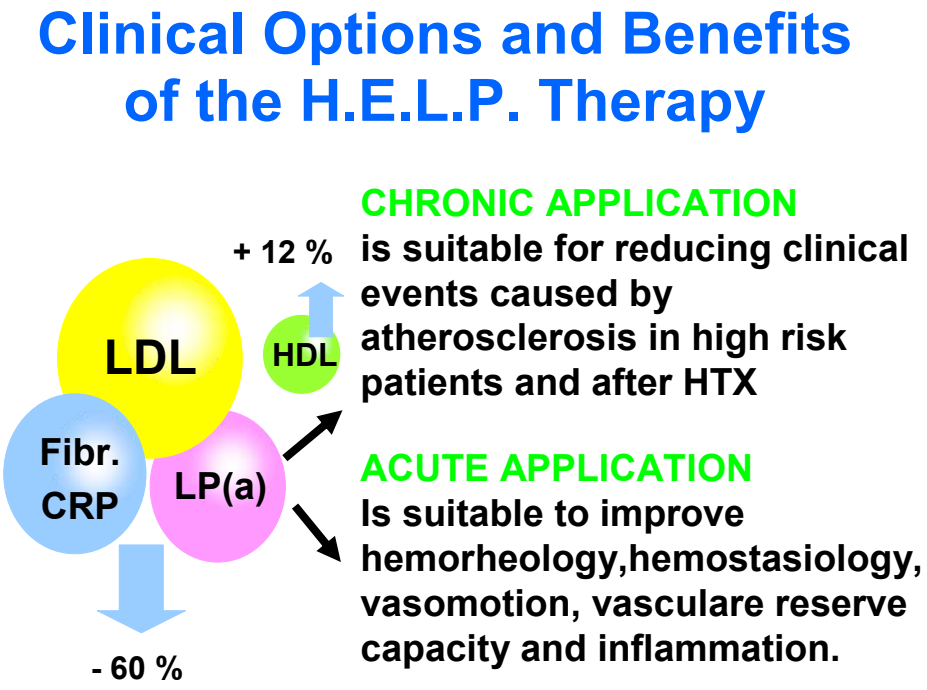


Fig. 37

(see specific literature attached)

Summary

The currently used H.E.L.P. system provided by B. Braun Melsungen (BBM) is well-accepted by the scientific and medical community and has proven its clinical utility. It differs from all other techniques by the simultaneous removal of LDL, Lp(a), inflammatory and procoagulatory factors.

(For more details see comprehensive literature for the H.E.L.P.-treatment)

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