B. Braun H.E.L.P. Apheresis
Plasmat® Futura Treatment System

The apheresis therapy – more than just LDL reduction

H. eparin-induced
E. xtracorporeal
L. DL
P. recipitation

B|BRAUN
SHARING EXPERTISE

Long tradition of competence and partnership
As a top healthcare company, B. Braun can look back on more than 170 years of tradition. Significant medical advances were first made possible by B. Braun products. The foundation stone of modern infusion technology, for example, was laid by the development of the Braunüle, the injection stopper that could be used multiple times, and the development of perfusors and infusomats.

B. Braun – Sharing expertise
Our promise to you.

Contents

H.E.L.P. Apheresis: Medical quality based on experience

B. Braun Avitum –
Expertise in extracorporeal blood treatment

As one of the world's largest complete systems providers in the field of extracorporeal blood treatment, the B. Braun Avitum division develops, manufactures and distributes products and services for the treatment of chronic, acute kidney failure and for therapeutic apheresis. B. Braun Avitum is also one of the largest operators of a comprehensive network of dialysis centers.

H.E.L.P. – Help and hope for your patients

H.E.L.P. apheresis (Heparin-induced Extracorporeal LDL Precipitation) is an extracorporeal blood cleaning procedure for the treatment of lipometabolic disorders which do not respond sufficiently well to conventional treatments.
H.E.L.P. is not only used in the case of severe forms of atherosclerosis, but also for rheological disorders (microcirculatory disturbance of the blood). This effective and selective procedure removes not only LDL cholesterol, but also additional risk factors with an arteriosclerotic effect (e.g. lipoprotein(a), fibrinogen, inflammatory factors). The procedure increases cardiac blood flow right into the capillary vessels with lasting effect and the frequency of coronary events is reduced. Patients report a subjective improvement in their general state of health, as well as a better quality of life.

H.E.L.P. apheresis is also efficiently used as a preventive and therapeutic measure in the case of transplant vasculopathy and for the treatment of acute hearing loss.

Our experience for your patients

H.E.L.P. is a unique apheresis system which has secure data on clinical effectiveness (outcome).
Out of a total of more than 350,000 individual treatments, 135,000 have been scientifically documented and evaluated.

H.E.L.P. has extensive experience, since more than 25 years, in the treatment of children with homozygous familial hypercholesteraemia.

H.E.L.P. is used in more than 15 countries worldwide and is licensed by the FDA in the USA.

In the development of extracorporeal blood cleaning procedures, B. Braun paved the way for LDL apheresis to become recognised as a therapeutic option for the treatment of severe lipometabolic disorders resistant to other therapeutic measures. Based on the ideas of H. Wieland and D. Seidel, H.E.L.P. apheresis was developed in cooperation with B. Braun during the period 1980 – 1983. Following initial preliminary experiments, the H.E.L.P. treatments began in 1985 as part of a proband study. The subsequent pilot study was successfully completed in 1987. In two multi-centre studies with public support, proof of the effectiveness and relevance of H.E.L.P. apheresis was finally provided between 1987 and 1994. In 1994, the procedure was licensed under pharmaceutical law as an approved therapeutic option embedded in the statutory benefit system.

Our principles for your treatment safety

Our mission statement

- An efficient apheresis system lowers atherogenic causal factors such as LDL cholesterol and Lp(a) as well as specifically atherogenic cofactors such as fibrinogen, triglycerides and VLDL cholesterol.
- An optimal apheresis system also selectively lowers proinflammatory parameters such as hsCRP as well as cell adhesion factors: E-selectin, V-CAM, I-CAM.
- An effective apheresis system must not interfere non-specifically with the plasma protein balance during chronic treatment.

Our success

- A modern, selective and therefore efficient apheresis system for the targeted reduction of atherogenic and proinflammatory risk factors.
- Our many years of experience in clinical practice and science. Our experience means that you and your patients can confidently place your trust in a safe and well-established therapeutic option.

In research, we insist upon convincing and reliable results. For your safety, for your competence, for your trust.

For 25 years: H.E.L.P.

Maximum therapy of atherosclerosis

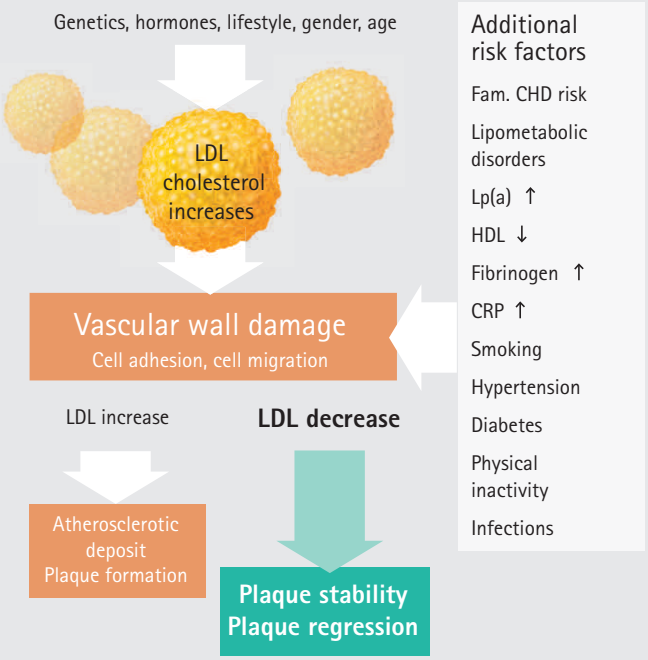
H.E.L.P. apheresis protects your risk patients
Heparin-induced Extracorporeal LDL Precipitation offers you a targeted option with lasting effect in the treatment of therapy-resistant patients with severe lipometabolic disorders and resultant symptoms. H.E.L.P. therapy is also used successfully for micro-circulatory disorders.

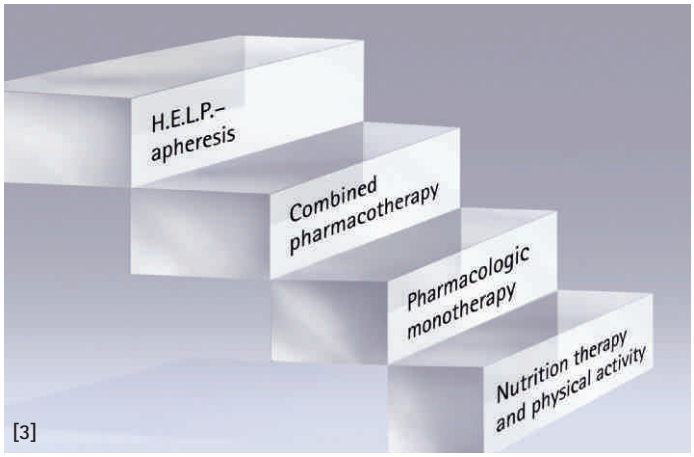
The highly selective H.E.L.P. procedure results in a direct plasma reduction of LDL cholesterol, Lp(a), LDL fibrinogen and C-reactive protein (CRP) of up to 80 percent.
H.E.L.P. therefore lowers your patients' lipid levels and eliminates the pathogenic causal factors of atherosclerosis.
Patients with coronary heart disease benefit particularly from H.E.L.P. therapy. These patients benefit from the additional reduction of fibrinogen and proinflammatory factors.
There is a notable improvement in coronary blood flow after just one treatment. Studies prove that:

H.E.L.P. lowers the risk of coronary events.

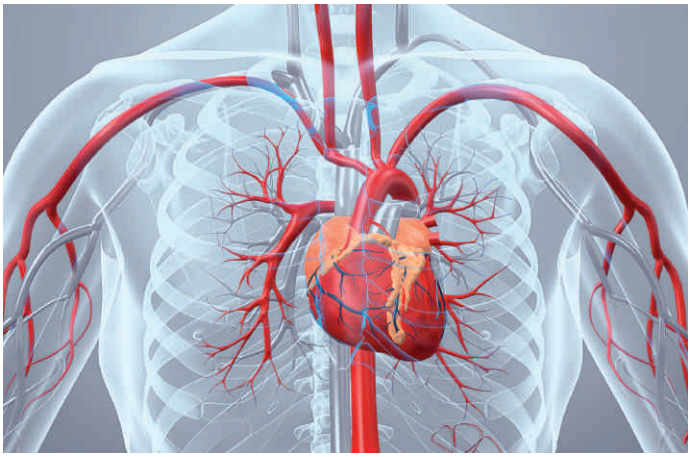
H.E.L.P. apheresis is an effective alternative and concomitant option to pharmacotherapy: for longer life expectancy and improved quality of life.

Atherosclerosis and CHD risk factors [35]

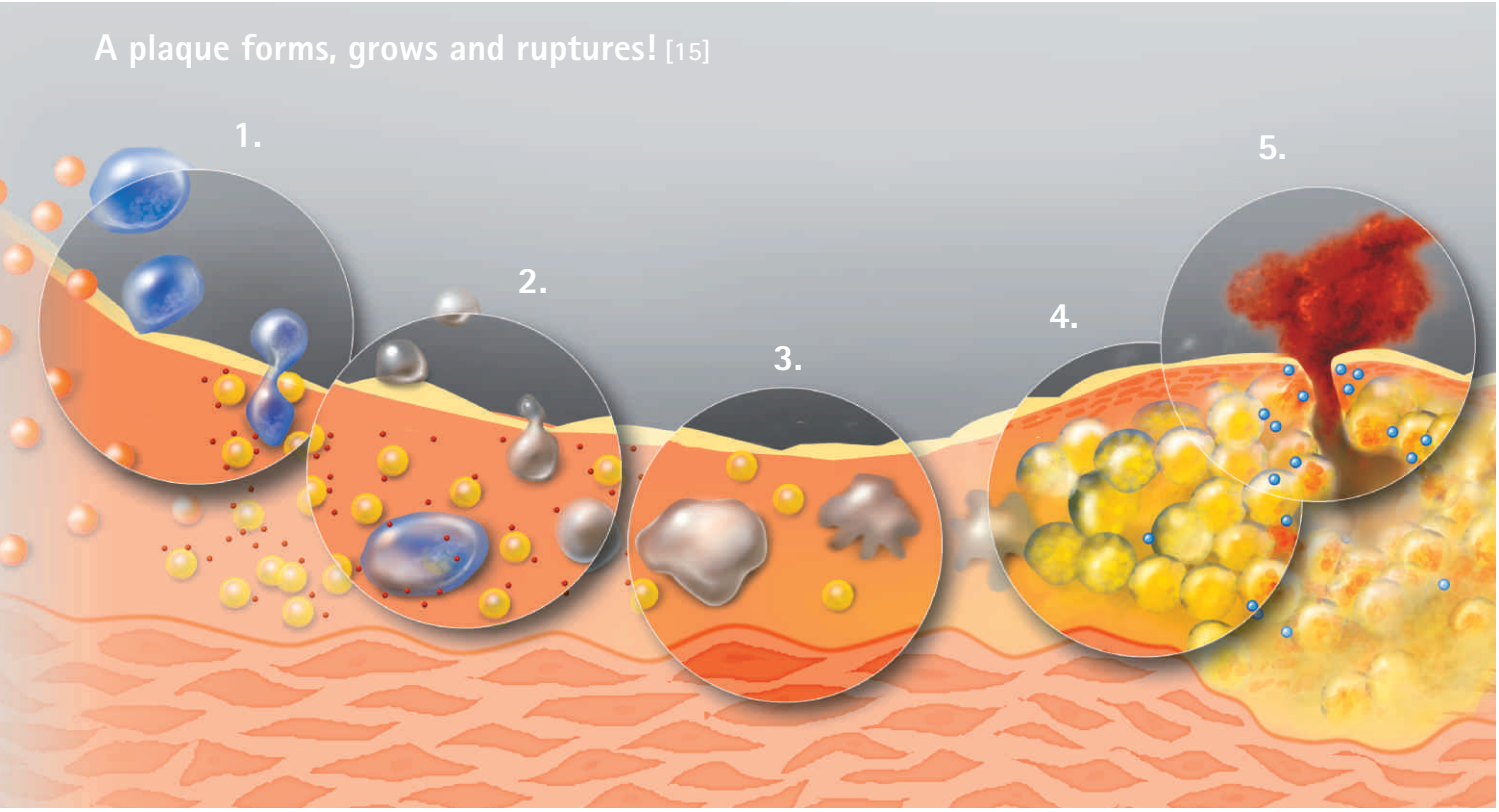




[3]



A plaque forms, grows and ruptures! [15]



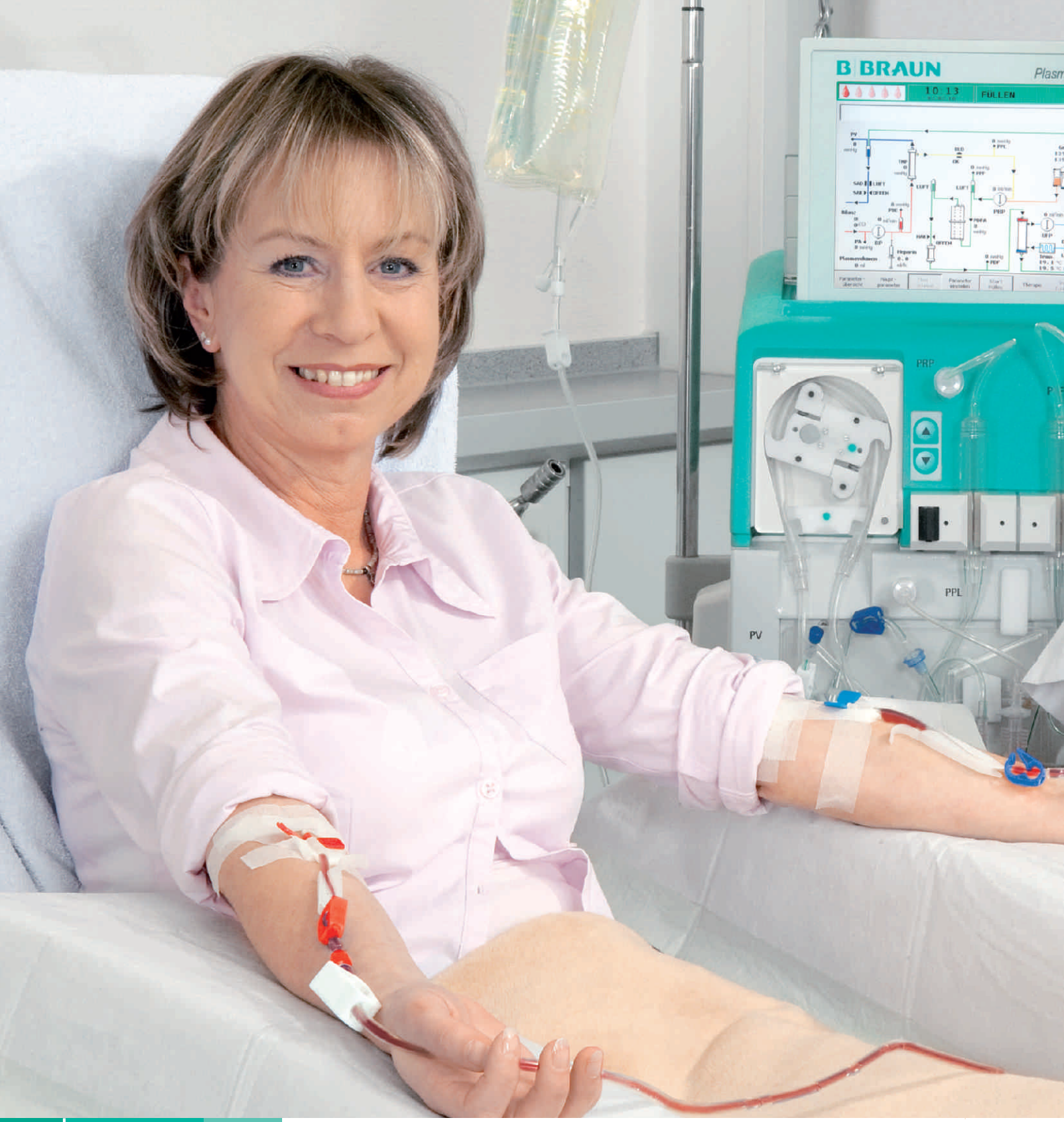
1. A plaque forms when excess LDL particles accumulate in the arterial walls and are chemically altered (oxidised). Endothelial cells then attract monocytes and T-cells using adhesion molecules before trapping these inside the inner layer with chemokines.

2. The monocytes then mature into macrophages, which with the T-cells, produce inflammatory mediators. Signal substances cause the macrophages to form molecular tools with which they can absorb the oxidised LDL particles.

3. The macrophages fill with fat droplets. Due to their appearance, these are now called foam cells. With the T-cells, they form lipid streaks, which are precursors of the plaque.

4. A fibrous, viscous, glutinous cap of smooth muscle cells and collagen forms over the lipid core and this isolates the inside of the plaque from the blood stream.

5. If a damaged plaque ruptures, this causes the tissue factor produced by the foam cells to emigrate. This has high potential to initiate the coagulation cascade. A thrombus forms immediately – there is the threat of an infarction.



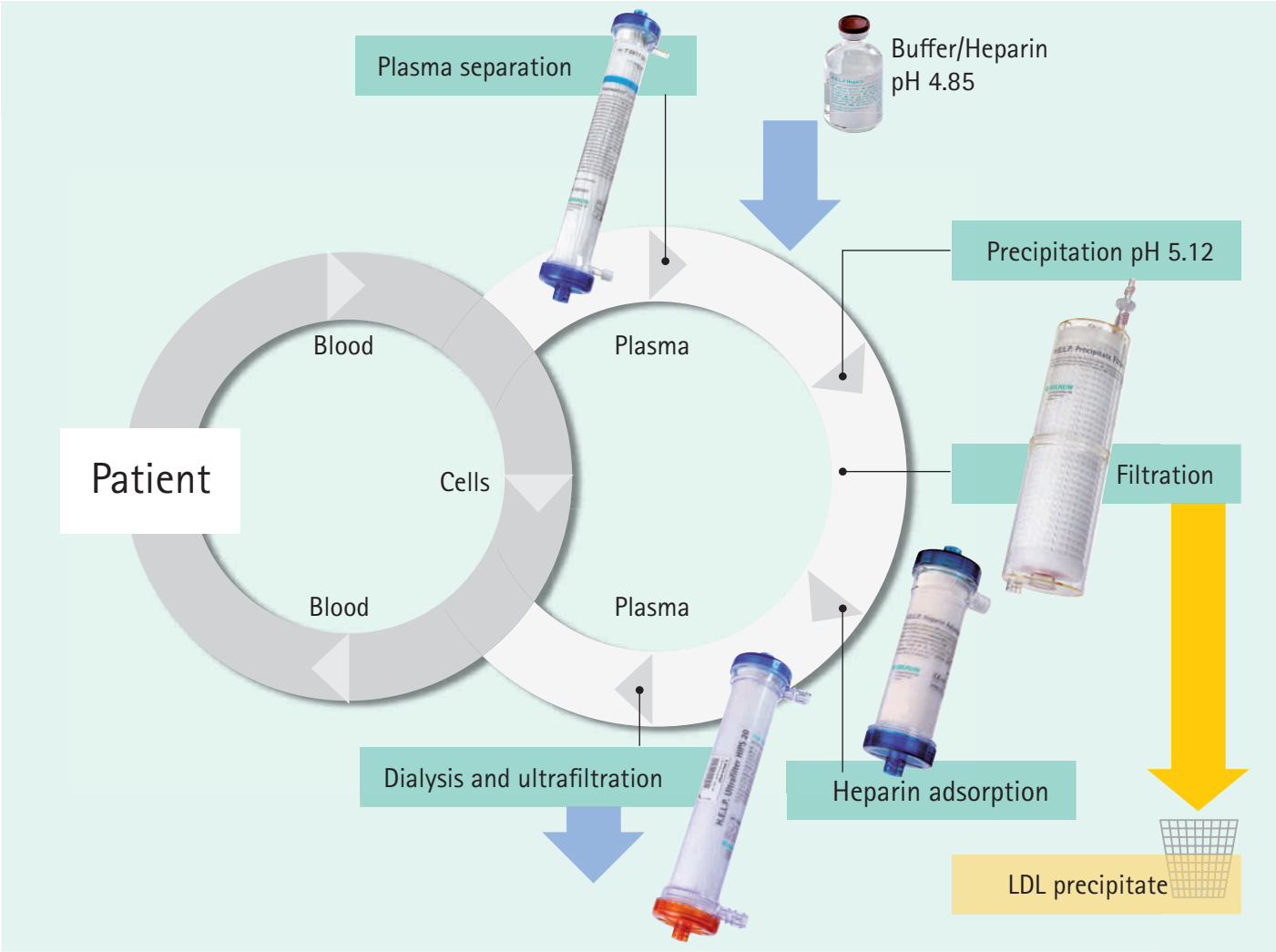
H.E.L.P. Apheresis.
Efficient. Selective. Unique

Ultimate therapeutic option in the treatment of severe lipometabolic disorders

H.E.L.P., Heparin-induced extracorporeal LDL/Lp(a)/Fibrinogen Precipitation, is a blood cleaning procedure which can be used to treat severe lipometabolic disorders which do not respond sufficiently well to conventional measures. The H.E.L.P. procedure also offers long-lasting effects.

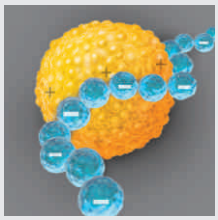
H.E.L.P. LDL apheresis is performed automatically by the Plasmat® Futura by means of plasma modulation. Through plasma separation, the patient's plasma is separated from the other blood constituents. The separated plasma is mixed with an acetate buffer saturated with heparin.

The degree of acidity of the plasma (pH) is thereby lowered to 5.12. At this value, LDL cholesterol, Lp(a), fibrinogen and the proinflammatory factors are selectively precipitated out of the plasma. Together with the heparin additive, the separated constituents form insoluble precipitates which can be removed from the plasma in a single filtration stage.
The unused, excess heparin is then retained by an adsorber, and the physiological level of the purified plasma is restored by means of bicarbonate ultrafiltration. The selectively treated, purified plasma is then remixed with the remaining blood constituents and supplied back to the patient.



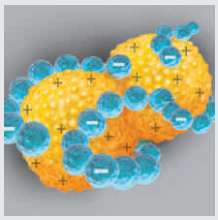
H.E.L.P. helps – based on sound principles, efficient, safe and with lasting effects

Steps in the precipitation

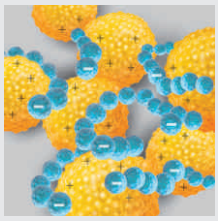


LDL and heparin at the physiological pH value

At a pH value of 5.12, the charge properties of LDL change. The result is the creation of additional positive charges.

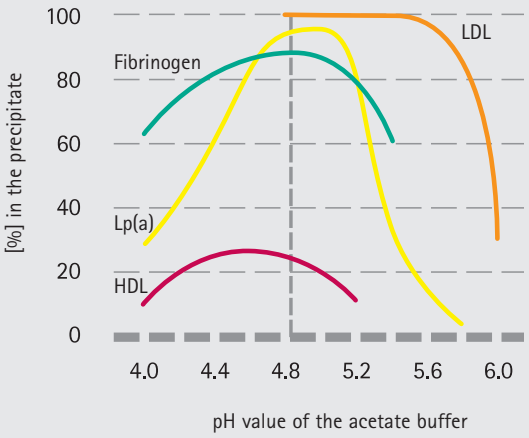


These altered charge properties result in a stronger association of LDL and heparin.

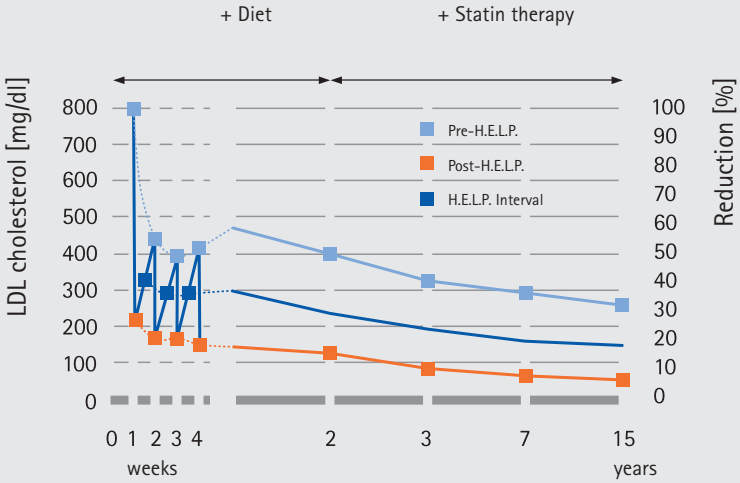


The increased cross-linking in the course of the reaction results in the formation of the LDL-heparin precipitate.

Precipitation response in relation to pH value [2]



H.E.L.P. therapy has lasting effects: LDL development



Patient (female) with homozygous familial hypercholesteraemia [35]

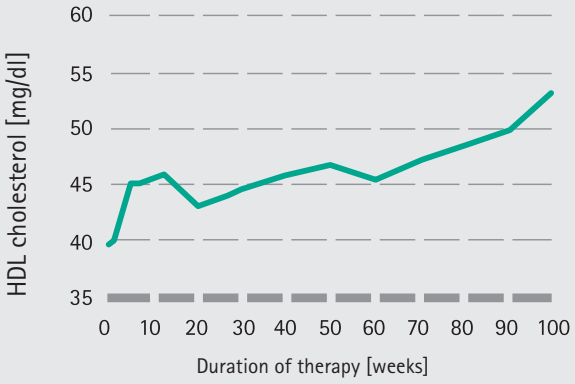
H.E.L.P. therapy is characterised by selectivity and a high degree of effectiveness:

H.E.L.P. enables the effective and simultaneous elimination of LDL cholesterol, Lp(a) and fibrinogen. Additional proinflammatory factors, such as hs C-reactive protein, and the cell adhesion molecules E-selectin, I-CAM and V-CAM-1 are also lowered. The plasma globulins are not affected.

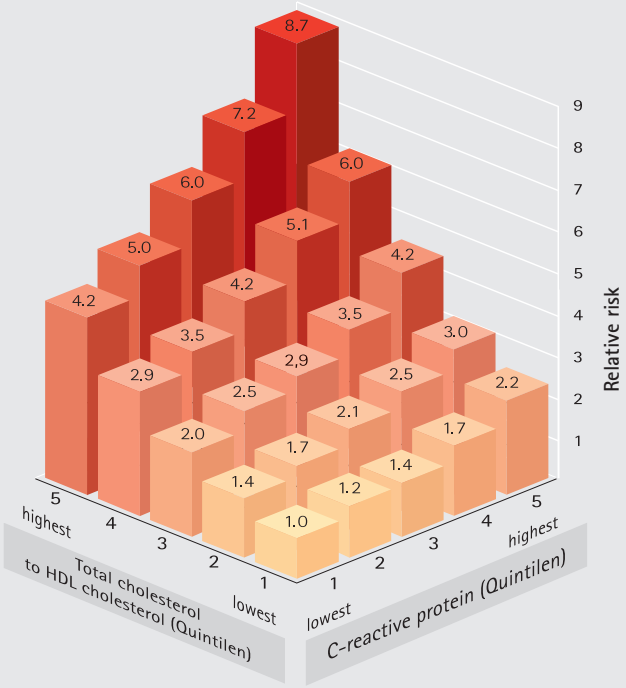
With chronic treatment, HDL cholesterol increases in the therapeutic interval.

H.E.L.P. apheresis with the Plasmat® Futura is a safe and effective procedure which does not put too much strain on the patient and which is well tolerated. There are no contra-indications for primary drug therapy. Well-documented long-term studies provide evidence of the high clinical effectiveness of the therapy.

HDL development



Effect of regular H.E.L.P apheresis on HDL [n = 50] **[34]**



Relationship between LDL-C level and inflammation **[31], [32]**

Effective and safe

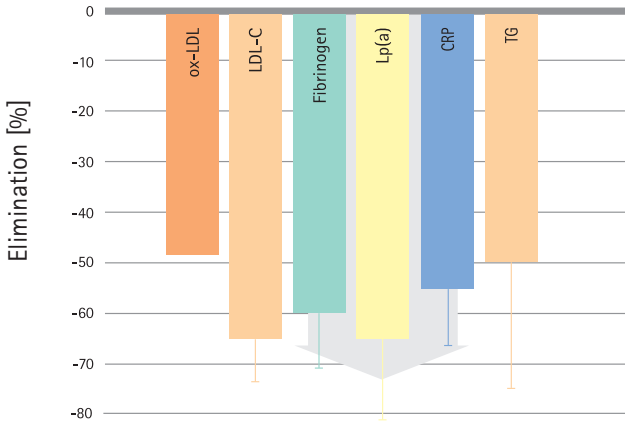
In addition to LDL cholesterol, Lp(a) and fibrinogen, there are other constituents in blood plasma which contribute towards the development of atherosclerosis.

H.E.L.P. also lowers proinflammatory factors such as C-reactive protein and molecules which promote the adhesion of inflammatory cells to the vascular wall, such as E-selectin, V-CAM-1 and I-CAM.

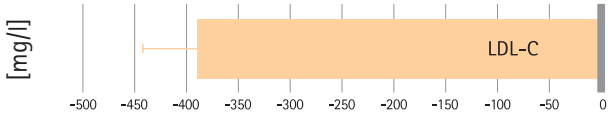
In most cases, H.E.L.P. therefore acts as a preventive measure against the progression of atherosclerosis. The frequency of possible resultant coronary events is therefore successfully reduced.

Benefits of H.E.L.P. therapy

- Removes the risk factors of atherosclerosis effectively
- Minimises the frequency of coronary events
- Has long-lasting effects for a wide range of indications
- Is scientifically documented



Average reduction of specific plasma constituents by one-time H.E.L.P. treatment with 3 l plasma volume



Reduction in LDL-C in mg per litre of treatment volume

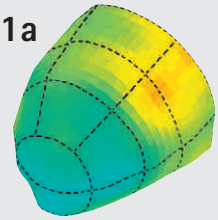
[13], [17], [23], [27]

H.E.L.P. Apheresis with the Plasmat® Futura

H.E.L.P. increases cardiac blood flow

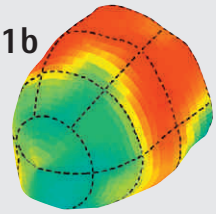
1. H.E.L.P. treatment

1a



Heart muscle blood flow before H.E.L.P. treatment

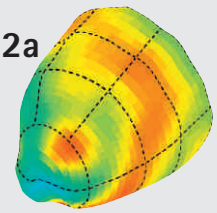
1b



Heart muscle blood flow 20 hours after H.E.L.P. treatment

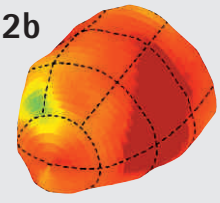
after 9 months of H.E.L.P.

2a



Heart muscle blood flow before H.E.L.P. treatment

2b



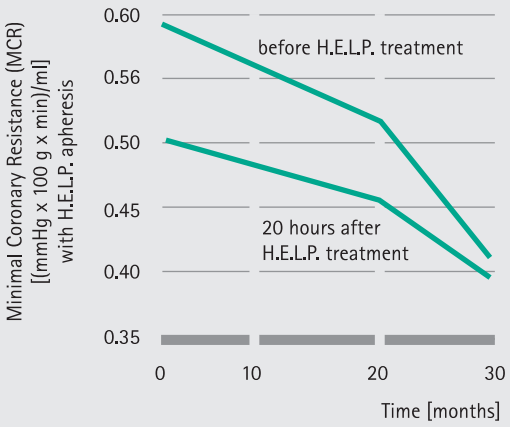
Heart muscle blood flow 20 hours after H.E.L.P. treatment

weak blood flow — strong blood flow

The coronary blood flows were determined using Positron Emission Tomography (PET) following the infusion of adenosine for maximum vascular distension.

[20], [21], [22]

H.E.L.P. improves the regulation of vascular distension

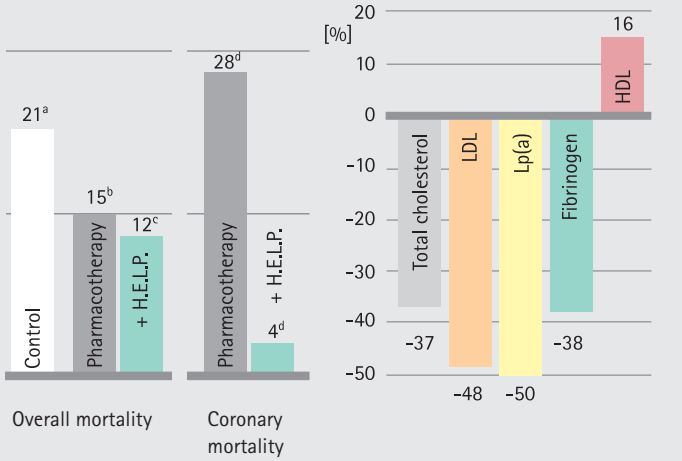


Evidence of the improved coronary perfusion as a result of chronic H.E.L.P. therapy is also provided by the reduction in Minimal Coronary Resistance (MCR) [Positron Emission Tomography]. **[21]**

H.E.L.P. therapy results in:

- Reduction of the lipoprotein level
- Reduction of the oxidative stress at the cellular level
- Reduction of the fibrinogen
- Reduction of the proinflammatory plasma proteins such as hsCRP and homocysteine
- Reduction of the cell adhesion molecules V-CAM-1, I-CAM and E-selectin
- Positive effect on the endothelial inflammation processes
- Positive effects on microvascular atherosclerosis

For a longer life and improved quality of life



Duration of treatment 5 years, [a]n = 2223, [b]n = 2221, [c]n = 829, [d]n = 186 **[35], [10]**

Change in specific plasma constituents after 16 months of H.E.L.P. therapy [n = 44] **[27]**

H.E.L.P. has long-lasting effects:

- Secure data shows the reduction in the overall mortality of the patients undergoing H.E.L.P. apheresis. On average, H.E.L.P. patients have a longer life expectancy than patients with the same risk profile undergoing conventional therapy.
- The level of serum lipoproteins drops with lasting effect on a weekly average. Compared to patients not undergoing apheresis and when combined with the required drug therapy, the target values set by the specialist associations are almost completely achieved in the case of high-risk patients.

H.E.L.P. – High clinical effectiveness

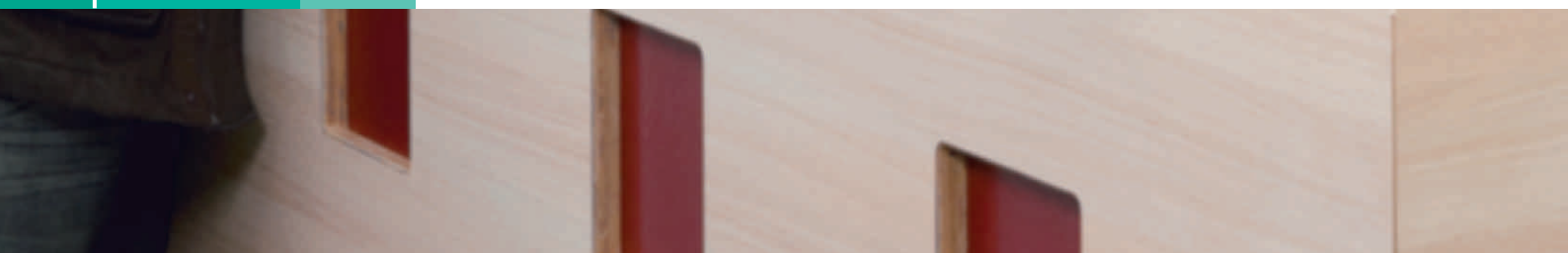
As a result of the reduction of atherosclerosis risk factors (LDL, Lp(a), fibrinogen), in many cases the deposits in the vessels are also reduced. Deposited cholesterol is flushed out. As a result, the blood vessels often regain their original capacity to regulate vascular distension (see figure on left). The blood flow through the tissue improves. The patient feels "fitter" – and this is not just subjective.

Proinflammatory plasma proteins [24]

Acute percentage reduction (%)

Marker	HELP
MCP-1	-15
ET-1	-25
LBP	-27
Lp-PLA$_2$	-22
VCAM-1	-20
ICAM-1	-10
E-Selectin	-31
Fibrinogen	-65
Ox-LDL	-65
CRP	-65

Indications –
more that just LDL reduction



The H.E.L.P. treatment has proved a success with severe lipometabolic and microcirculatory disorders. Publications about the following treatment mode are existant:

- Familial hypercholesteraemia in homozygous and heterozygous form
- Hyperlipoproteinaemia (a)
- PAOD
- Acute hearing loss
- Age-dependent macular degeneration
- Ischaemic optic neuropathy
- Diabetic foot
- Transplant vasculopathy
- Coronary bypass operation
- Pre-eclampsia

Efficient and selective treatment of:

Lipometabolic disorders

Familial hypercholesteraemia

Patients with severe lipometabolic disorders that cannot be controlled sufficiently by diet and medication in secondary hypercholesteraemia. Despite maximum treatment by diet and medication, the plasma LDL cholesterol concentration cannot be controlled sufficiently; there is a high risk of arteriosclerotic complications or manifest coronary heart disease.

Hyperlipoproteinaemia (a)

This occurs in cases of severely increased plasma concentrations of lipoprotein (a) (>60 mg/dl) and a high risk of arteriosclerotic complications or manifest coronary heart disease. In order to achieve optimum success with the H.E.L.P. apheresis treatment, lipid-reducing treatment by means of diet and medication should be retained.

Acute hyperlipidaemia or fibrinogenaemia

Patients with acute hyperlipidaemia or fibrinogenaemia, in whom an acute and effective reduction of fibrinogen, LDL cholesterol, VLDL cholesterol or lipoprotein(a) is indicated from a medical perspective. Treatment should only be applied after strict consideration of individual benefits/risks.

Microcirculation disorders

Acute hearing loss

Patients with acute hearing loss (hearing loss ≥ 15 db in 3 frequency bands in the affected ear in relation to the non-affected ear), if the treatment is commenced within 7 days, although at the latest 6 weeks after the onset of the event.

Rheological diseases

Patients with diseases which stem from disorders of the blood flow properties (rheological diseases) in whom an improvement in microcirculation via extracorporeal blood treatment by changing the composition of blood components is indicated from a medical perspective.

Familial hypercholesteraemia
LDL apheresis

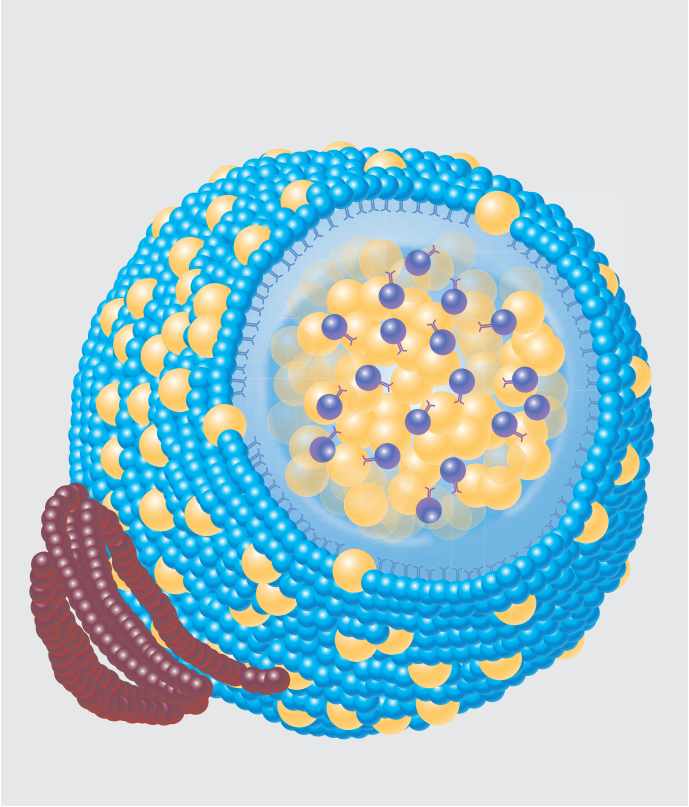
Increased cholesterol values are one of the most frequent causes of cardiovascular diseases. The increase in cholesterol values can be down to lifestyle or can be the secondary consequence of poorly controlled type II diabetes mellitus or metabolic syndrome. In these cases, conventional treatments are sufficient.
An increase can also be caused by a genetic defect. In carriers, the receptors for LDL cholesterol are often damaged and the function of the processing of the LDL is limited. We then talk of familial hypercholesteraemia (FH). This disease is transmitted as dominant and can often not be treated sufficiently using conservative methods. Without treatment, adults have an 84 % higher risk of developing an atherosclerotic complication.
If all LDL receptor genes are defective, it is a case of **homozygous** familial hypercholesteraemia. These patients have a cholesterol level of > 600 mg/dl and often suffer a myocardial infarction or stroke in early childhood. Life expectancy is then often less than 30 years if not treated. Treatment with medication is not enough: for such patients, apheresis is the only option for leading a normal life.

Heterozygous familial hypercholesteraemia occurs if the LDL receptor gene is only partially mutated. It is often only possible to reduce the LDL cholesterol level sufficiently in these patients by using apheresis.
The diagnosis is made on the basis of a patient's case history, a physical examination and his lipid profile. Ultimate certainty is provided by the evidence of the mutation of the LDL receptor gene. The aim of the treatment is the long-term prevention of further atherosclerotic complications. If diagnosis and treatment are made in good time, patients with familial hypercholesteraemia can avoid serious late-onset cardiovascular diseases.
H.E.L.P. apheresis is mainly used to treat patients with familial hypercholesteraemia for whom conservative treatment options do not achieve the desired reduction of LDL cholesterol. The high selectivity of the H.E.L.P. apheresis treatment makes it possible to remove atherogenic plasma components from the blood in a targeted manner. The non-specific removal of other, non-pathogenic plasma components is thus avoided.

Hyperlipoproteinaemia
Lp(a) apheresis

Lp(a) apheresis

Lipoprotein(a), strongly related to the LDL cholesterol, is an independent risk factor in a number of atherosclerotic diseases. The role of this plasmalipoprotein in the development of a stroke (apoplexy) and the occlusion of the vascular arteries (peripheral arterial occlusive disease, or PAOD) has now been confirmed. An atherosclerotic complication with Lp(a): the involvement of lipoprotein(a) in most cases accompanies a severe inflammatory reaction on the vascular endothelium. It is not yet possible to use drugs to influence Lp(a). Valid studies have now shown that only Lp(a) apheresis drastically reduces the rate of coronary events in patients with markedly increased Lp(a) and diagnosed atherosclerosis.



H.E.L.P. reduces Lp(a) effectively.

H.E.L.P. has a lasting influence on the rate of coronary events in patients with increased Lp(a) by reducing both Lp(a) and the parameters governing vascular inflammation.

Göttingen Risk, Incidence and Prevalence Study GRIPS

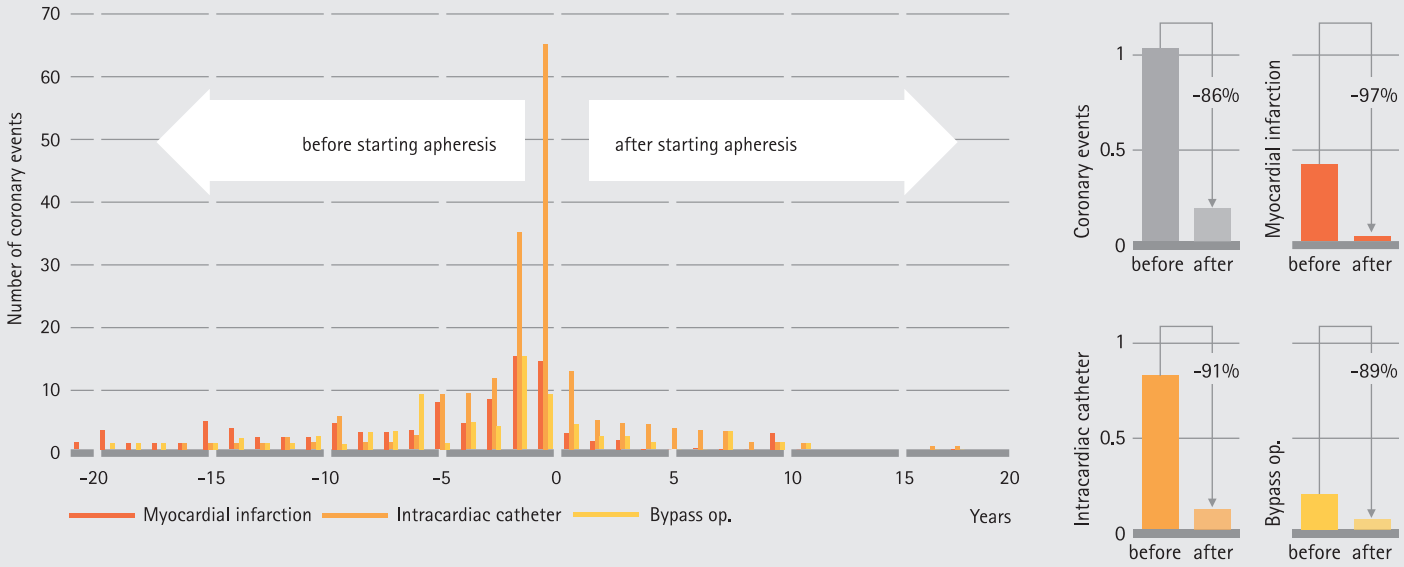
Prospective cohort study:	5790 men 40-59 years at the start of the study	
10 year follow-up:	299 MI, 259 chronic CHD 101 strokes, 168 cases of PAOD	
Risk factor Lp(a)	Lp(a) ≥ 29 mg/dl	
Relative risk (95% CI)	Myocardial infarction CHD PAOD Stroke	2.3 (1.9-2.9) 1.9 (1.5-2.4) 2.0 (1.4-2.7) 1.7 (1.1-2.6)

Lipoprotein (a)
Atherogenic properties

- Binding to fibrin and extracell. matrix
- Modulation of the fibrinolysis (competitive inhibition and plasmin development)
- Stimulation of growth and the migration of smooth muscle cells (activation inhibitor of TGF-b)
- Reinforcement of monocyte adhesion and migration (PKC-dependent activation)
- Influencing of the inflammatory reaction

Hyperlipoproteinaemia (a)

Reduction of the rate of individual coronary events before/after apheresis



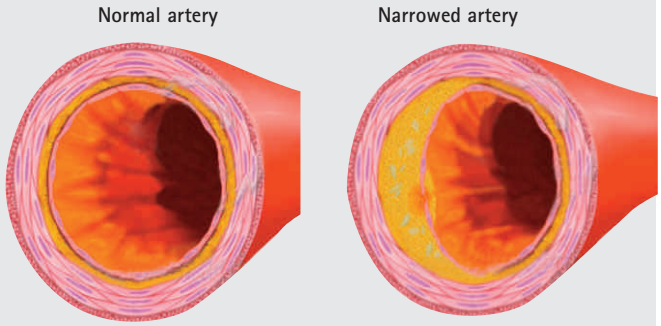
Reduction of the rate of coronary events before/after apheresis in patients with increased Lp(a) assessment of various apheresis methods. Percentage H.E.L.P.: 40 % **[9]**

H.E.L.P. therapy results in

- Reduction of the lipoprotein(a) level
- Reduction of the oxidative stress at the cellular level
- Positive effect on the endothelial inflammation processes
- Positive effects on microvascular atherosclerosis
- Reduction of thrombotic factors by:
  1. Reduction of the fibrinogen
  2. Reduction of the proinflammatory plasma proteins such as hsCRP
  3. Reduction of the cell adhesion molecules V-CAM-1, I-CAM and E-selectin

Acute hyperlipidaemia and fibrinogenaemia

Lp(a) – PAOD – stroke



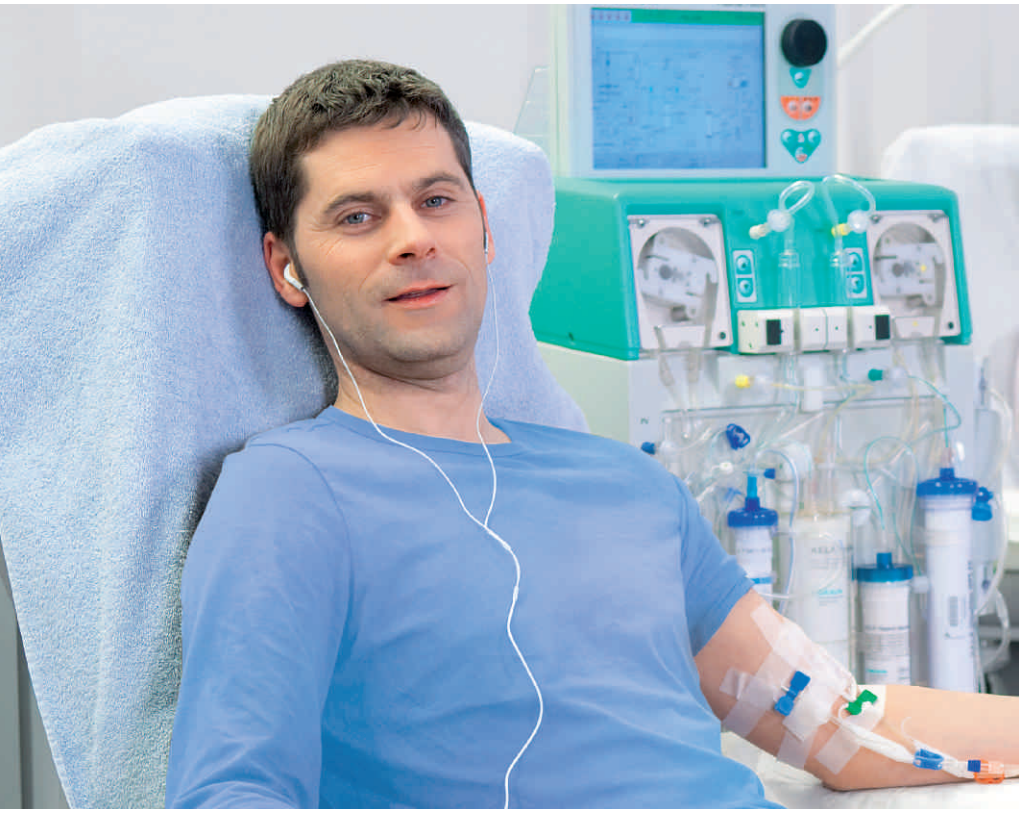
Development of atherosclerotic deposits in the extremities due to intermittent claudication ("window shopper's disease")

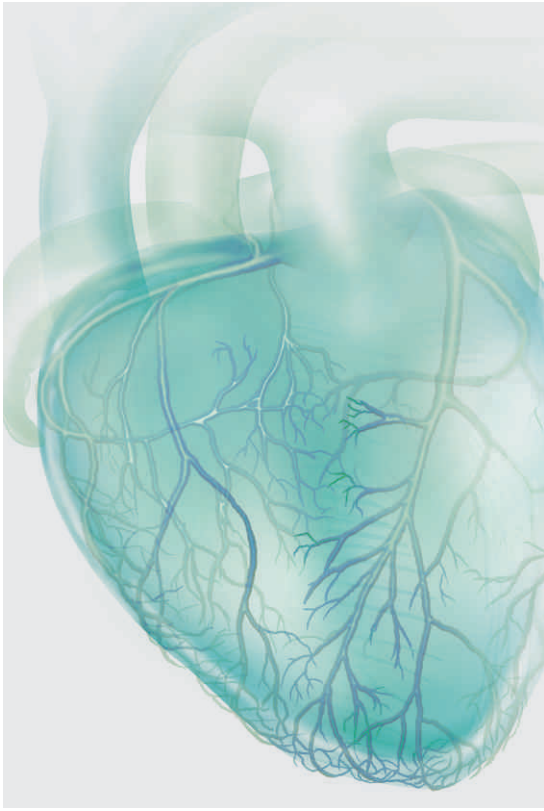
Improvement of walking distance in patients with intermittent claudication ("window shopper's disease") [30]

Parameter	Pre-apheresis	Post-apheresis
Total walking distance (metres)	79±60	194±80
Pain-free walking distance (metres)	60±52	173±76

Peripheral arterial occlusive disease (PAOD), also called window shopper's disease, is one of the most frequent vascular diseases in everyday clinical life. The frequency of PAOD is age-dependent, increasing as you get older. Possible risks of this disease include amputations and serious secondary diseases such as strokes or myocardial infarctions. Pains in the legs force patients suffering from peripheral arterial occlusive disease to stand still frequently, as if they were window-shopping. The pains are caused by circulation disorders, which occur as the consequence of narrowed leg arteries. Generally speaking, 90 % of patients with advanced-stage PAOD also have affected coronary arteries, and 70 % of patients affected carotid arteries, in addition to the affected leg arteries.

Acute hyperlipidaemia or fibrinogenaemia

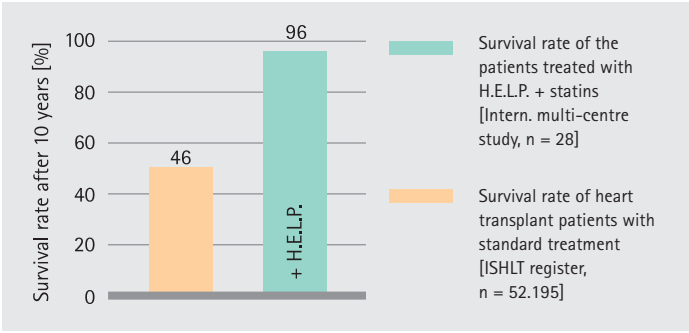




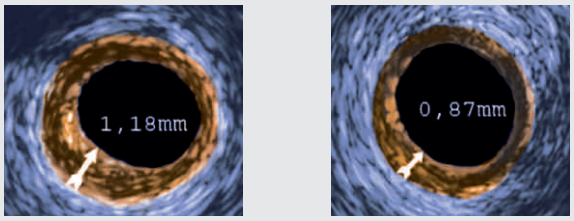
Transplant vasculopathy (TVP) is the most significant long-term complication following a successful heart transplant. So-called chronic rejection of the transplanted organ is triggered or maintained by immunological processes. It is to be assumed that all damage to the coronary vessels (e.g. by rejection reactions, infections, increased blood serum lipid values) increases the intensity of this disease. According to scientific findings, 5-10 % of heart transplant patients per year show signs of this transplant vasculopathy, meaning that, after 5 years, 30-50 % of transplant patients are affected.

The primary aim of the medical profession is to prevent this transplant vasculopathy from the outset. This can be achieved above all by eliminating possible risk factors. The prevention of rejection reactions, the prevention or prompt treatment of viral infections, and the stabilisation of the blood serum lipids, blood sugar and blood pressure are significant preventative measures. Increased LDL cholesterol values should therefore be treated in a consistent and effective manner. H.E.L.P. treatment offers an effective option as a preventative measure. Using the H.E.L.P. method, it has been possible to document instances of regression using coronary angiography even in cases of advanced forms of TVP.

Transplant vasculopathy



Regression of a plaque by means of H.E.L.P.



Baseline

After 41 months of H.E.L.P. treatment

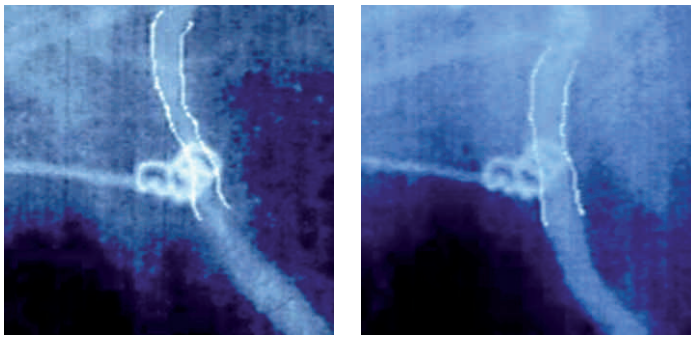
H.E.L.P. increases the survival rate following a heart transplant

Transplant vasculopathy is an accelerated manifestation of atherosclerosis. After the risk of rejection and infection, it is the most frequent cause of death amongst heart transplant patients. An international multi-centre study has now shown that the drastic reduction of fibrinogen, CRP and LDL cholesterol by a combination treatment of H.E.L.P. and statins considerably reduces mortality in cases of transplant vasculopathy: 10 years after the heart transplant, the survival rate of patients treated with H.E.L.P. and statins is 96 %.
With standard treatment, the survival rate in the same period is 46 % according to the International Society of Heart and Lung Transplantation (ISHLT).

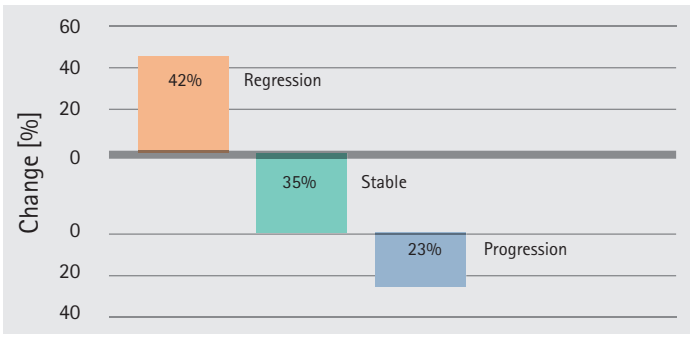
The images of graft atherosclerosis (RIVA) produced by means of intravasal ultrasound (IVUS) show the regression of a plaque after 41 months of H.E.L.P. treatment. [Casuistry]

After two years of H.E.L.P. treatment, the angiographic analyses showed a stable or regressive development for 77 % of the coronary segments with stenosis. [5]

Development of the stenosis grade under the influence of H.E.L.P.

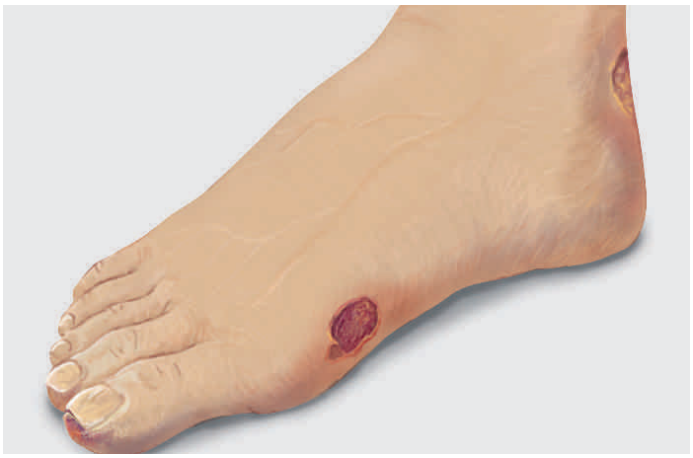


Regression of coronary stenosis in heart transplant patients in the second year after weekly H.E.L.P. treatment [26]



187 coronary segments in 33 patients after 2 years of H.E.L.P. treatment (limit value 4 %) [36]

Microcirculation disorders
Diabetic foot



Microcirculation disorders of the extremities (diabetic foot)

Diabetes mellitus can cause a great variety of indications. Circulation disorders in the lower leg or foot are a frequent secondary disease of diabetes. With diabetic angiopathy, even the slightest injuries caused by trauma or pressure can lead to the development of wounds on the extremity or calf, which heal badly and usually take several weeks. Due to the diabetic neuropathy - which is often concomitant - the injuries can occur easily and at times go unnoticed for a relatively long time due to the reduced pain sensation. With these wounds caused by microcirculation disorders, there is the risk that deep, hole-like skin ulcers (ulcerations) will grow deeper and deeper into the body part and will be colonised with multi-resistant organisms. A marked increase in the concentration of the acute phase protein fibrinogen was detected in this. There is an acute risk of blood poisoning. Only in rare cases is operative revascularisation technically possible.
Amputations of the extremities are frequently unavoidable in order to save the patients.

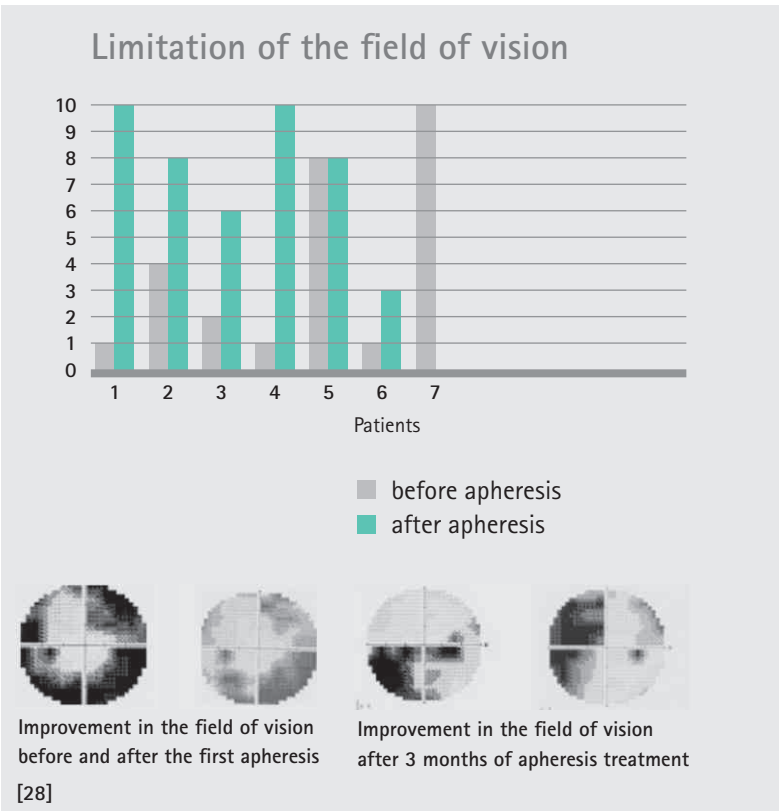
Documented effectiveness of the apheresis treatment

The H.E.L.P. method offers an effective treatment option for reducing the highly increased fibrinogen level and acutely improving the blood flow properties. In the context of a pilot study, pronounced leucocytosis was detected in the majority of those affected. Hyperlipidaemia was not evident. The H.E.L.P. treatment was able to significantly reduce the fibrinogen level in all patients. In a few cases, an improvement in cerebral functions could be established. Demarcation of the necrosis could be achieved with all patients.

Indications of microcirculation disorders caused by diabetes:

- Nerve damage
- Numbness, burning, pins and needles in the toes and feet.
- The feeling of walking on cotton wool as well as the feeling of having cold feet even though they are warm.
- Pain when resting feet, especially at night, and alleviation of pain by walking around or cooling.
- Swelling of the joints as well as a strong tendency to keratinisation and onychomycosis.
- Reduction or loss of temperature and pain sensation
- Circulation disorders
- Cold feet
- Thin, parchment-like, bluish-pale skin
- Pressure sores (reddish skin patches which cannot be brushed away)
- Calf pains or cramps on walking (alleviation by standing still)

Ischaemic optic neuropathy ("occular infarction")



Improvement in the field of vision before and after the first apheresis [28]

Improvement in the field of vision after 3 months of apheresis treatment

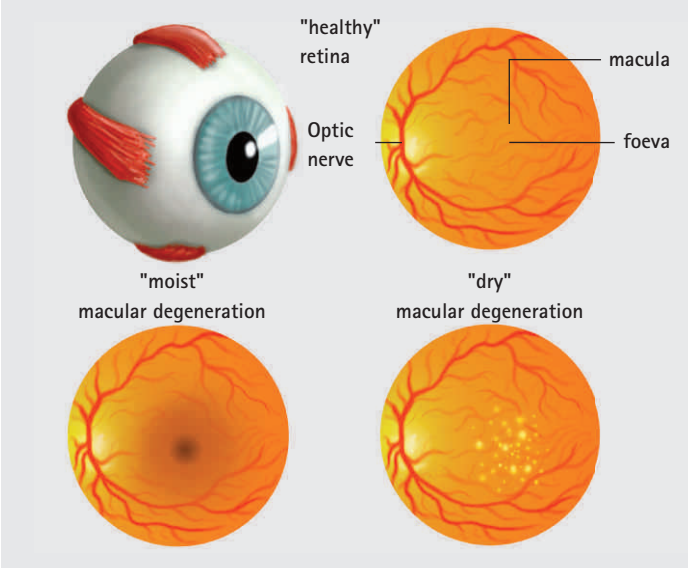
Ischaemic optic neuropathy ("occular infarction")

Ischaemic optic neuropathy, also termed "occular infarction" in general, is the acute occlusion of an occular artery supplying the optic nerve. As a rule, the main cause of ischaemic optic neuropathy is a vascular blockage due to atrial fibrillation, endocarditis or advanced atherosclerosis, which often occur as secondary diseases of diabetes mellitus. As a result, underperfusion of the head of the optic nerve and the resulting oxygen and nutrient deficiency damages the nerve fibres.

A significant indication of an occular infarction is the head of the optic nerve appearing not clearly demarcated and pale as a result of the oedema. Capillary vascular bleeding is visible in and around the optic disc.

The patient suffers a sudden loss of visual acuity in one eye, which also frequently reveals itself in the restriction of the field of vision (scotoma). If no treatment is sought, the patient can lose vision entirely in the affected eye within a few hours and go blind.

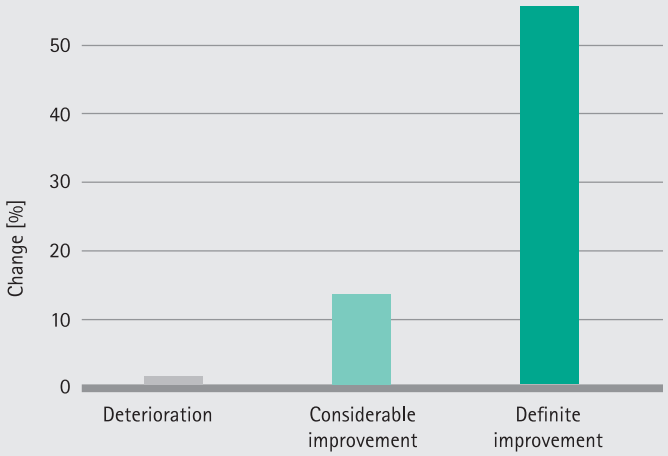
Microcirculation disorders
Age-dependent macular degeneration



Macular degeneration is understood as the decay of the tissue of the macula, the functional centre of the retina, which is responsible for the highest visual acuity as well as spatial vision within the retina. The decay of the macula can be distinguished as either a dry or a moist form of macular degeneration; the latter is also referred to as an exsudative form. 85 % of those affected by macular degeneration suffer from dry macular degeneration. In this disease, a metabolic disorder of the retina occurs in the region of the retina, causing increased deposits of metabolic end products, the so-called drusen. This is accompanied by circulation disorders and changes of nerve functions. These functional disorders in the retinal pigment epithelium (RPE), a cell layer which lies below the visual cells and is responsible for their perfusion, leads to increasingly greater

Vision with age-dependent macular degeneration.

Change of visual acuity following H.E.L.P. [1]

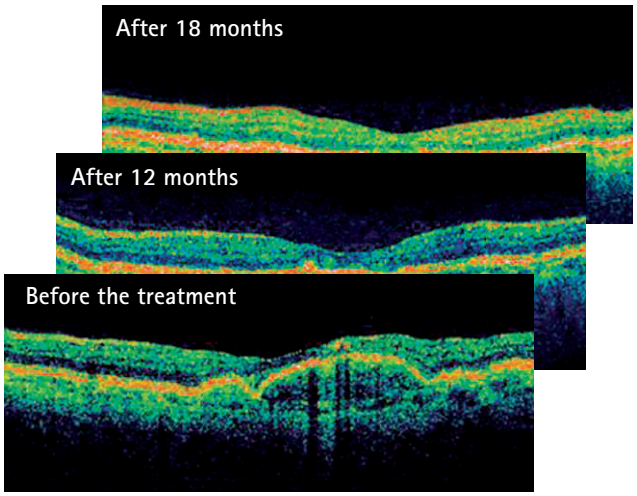


15 % considerable improvement
0 % considerable deterioration
55 % definite improvement

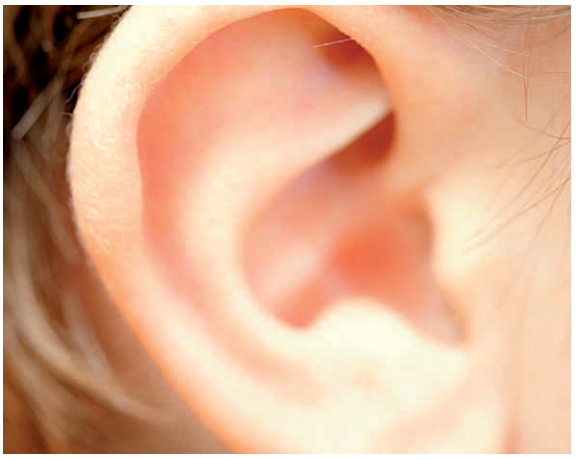
19 patients each with 8 sessions of treatment over 16 weeks

functional losses and later to cell death in the region of the external retinal and choroid layers. Often pathological cellular/vascular vegetations accompany macular degeneration, which also limit macular functions. The decay often leads to the complete loss of visual functions in the macula and it can also cause severe impairment in the regions around the macula. With the functional loss of the macula, the visual centre in the brain lacks information about the appearance of the surroundings.
A sharp picture can no longer be produced; vision is limited over the entire field of vision. In the advanced stage, the patient's capacity for orientation can be lost and the patient is no longer able to find his way about his surroundings without help.

OCT results



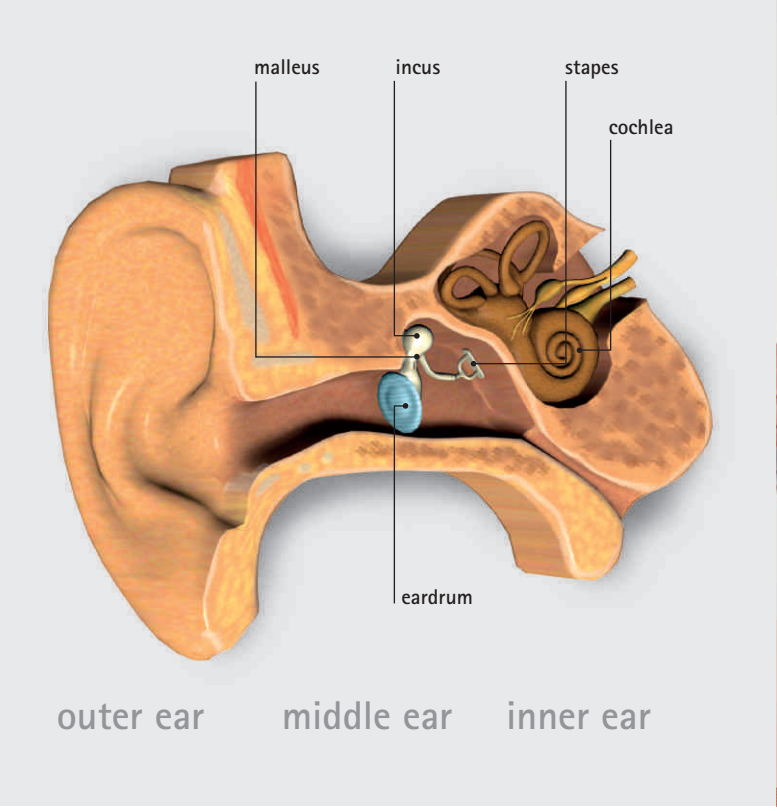
There is evidence that H.E.L.P. eliminates the deposits ("drusen") in the macula, with visual acuity improving after apheresis treatment. [1]



Acute hearing loss

With acute hearing loss, the electrical impulses are no longer forwarded to the brain as the sensitive hair cells are undersupplied in the cochlea.

Acute hearing loss



With acute hearing loss, the electrical impulses are no longer forwarded to the brain as the sensitive hair cells are undersupplied in the cochlea.

Sudden acute hearing loss and roaring in the ear

Acute hearing loss is a dysfunction of the inner ear and mainly occurs with no identifiable cause and without warning. Suddenly one is only able to hear very badly or even not at all in one or both ears.
Those affected report a dull noise, which can also be accompanied by whistling or a feeling of dizziness.

Probably the most frequent cause is a regional circulation disorder in the inner ear. The hair cells in the ear, which are responsible for hearing, react with extreme sensitivity if they are not sufficiently supplied. This is how acute hearing loss occurs.

If the acute hearing loss is not treated immediately, tinnitus – a permanent whistling sound in the ear – is the most frequent lingering delayed after-effect. In the worst-case scenario, hearing can no longer be restored. It is therefore extremely important that the patient seeks medical help immediately.

If circulation in the inner ear is restored again quickly in patients with acute hearing loss, the hair cells recover in most cases. That means: the earlier treatment is commenced, the greater the chances of a recovery.

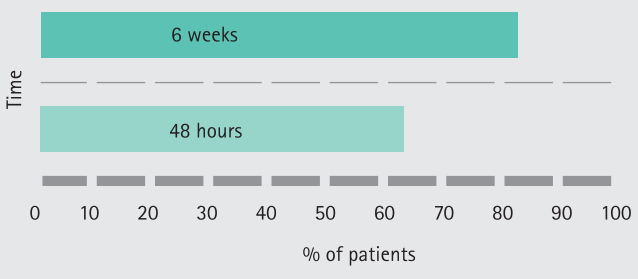
Patients with an increased cardiovascular risk (e.g. concerning heart and vessels) are susceptible to strokes and myocardial infarctions. They also more frequently suffer acute hearing loss, tinnitus or chronic inner ear deafness. This is not surprising because these illnesses stem from the underperfusion of an organ.

The blood purification method

There exist many very varied treatments. Use of H.E.L.P. apheresis to treat acute hearing loss is well documented in the scientific literature. It has proven clinical effectiveness and, compared with the standard treatment, is associated with little expenditure of time.

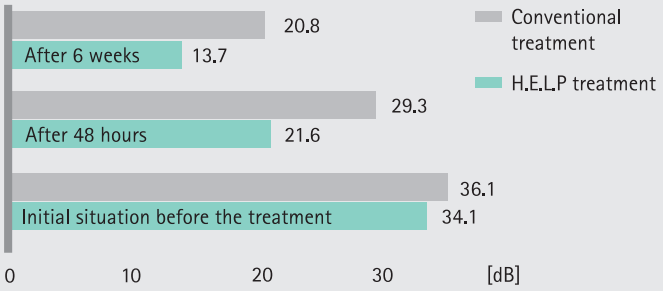
The H.E.L.P. method is certainly amongst the most promising treatments. In the event of acute hearing loss, the H.E.L.P. treatment only has to be carried out once on an outpatient basis.

Remission values with the H.E.L.P. treatment [38]

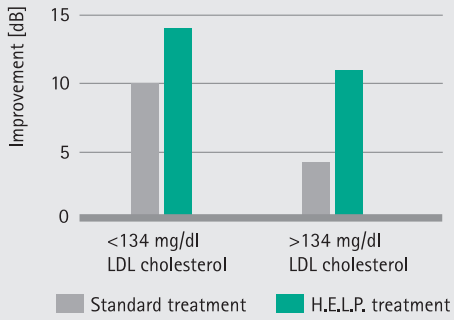


Acute hearing loss

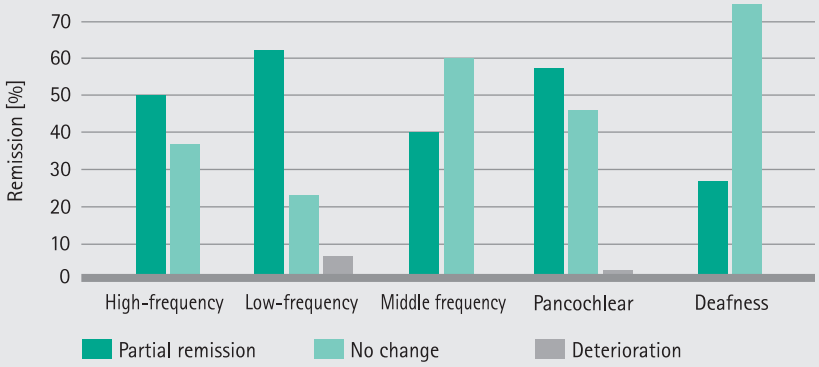
Speech audiogram [38]



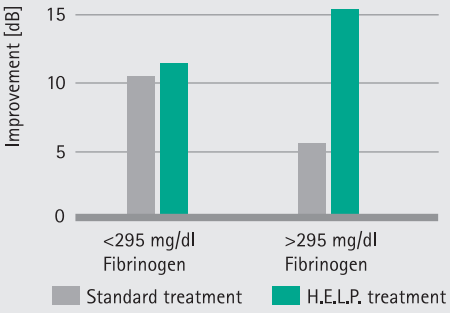
LDL cholesterol [38]



Remission values with H.E.L.P. treatment [6, 8]



Fibrinogen [38]



Assessment of the pure tone audiogram 2 weeks after apheresis with regard to the type of hearing loss

H.E.L.P., the scientifically proven successful method in the event of acute hearing loss

Several extensive scientific studies have proven the success of the treatment with acute hearing loss (Suckfüll et al. 2002: Fibrinogene and LDL apheresis in treatment of sudden hearing loss: a randomised multicentre trial. The Lancet, Vol. 360, no. 9384, p. 1811-1817). Experience shows that, with the majority of patients, hearing improves considerably as early as during the treatment or shortly afterwards.

It is important that treatment begins as soon as possible after the acute hearing loss is detected. However, even up to 6 weeks after the onset of acute hearing loss, the success of the H.E.L.P. treatment is still promising. In order to increase its success level even further, stress, excitement and noise must be avoided at all costs. The patient should relax, rest and simply switch off.

The risk factors that can contribute to the development of an acute hearing loss include:

- Overweight
- Increased blood serum lipid values
- Lipometabolic disorders
- Heart diseases
- Blood pressure fluctuations
- Increased tendency of the blood to clot
- Stress

Questions and answers

What is acute hearing loss?
Sudden inner ear deafness, which can be accompanied by tinnitus and dizziness.

When should I see my physician?
As soon as possible! Acute hearing loss requires urgent treatment. The sooner you react, the greater your chances of recovery.

How do I recognise acute hearing loss?
You will probably notice a reduction in your hearing. However, initially you may possibly only feel pressure and hear a whistling sound in your ear.

What are the causes of acute hearing loss?
The causes that can contribute to the development of acute hearing loss are varied and have not yet been sufficiently explained. The following are suggested in particular: a circulation disorder in the inner ear, autoimmune processes and viral infections.

What treatment options are there?
The treatment options extend from psychotherapy and a lengthy hospital stay right through to operations. H.E.L.P. is an alternative which facilitates an improvement in the symptoms within the shortest time possible.

Which treatment is the best one for me?
Acute hearing loss is not always the same. Together with your physician, you must decide which is the right treatment for you. All individual conditions and circumstances must be taken into account here.

Who pays for the treatment?
Contact your health insurer and ask if it will meet the costs for the relevant treatment.

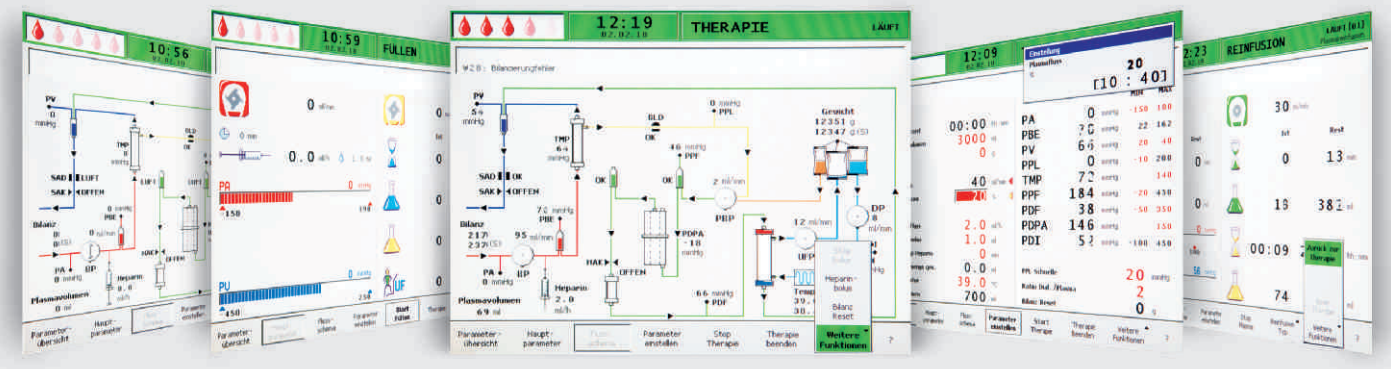
Plasmat® Futura monitors and controls

Plasmat® Futura – user-friendly treatment control, guaranteed

A complex treatment should be performed easily and reliably. The H.E.L.P. apheresis with Plasmat® Futura fulfills this requirement: It is easy to use and maintenance is reduced to a minimum. The user-friendly treatment control reduces familiarisation time and makes the system easier to operate.
The comprehensive in-depth product training provided to physicians and nursing staff by our experienced and qualified employees gives them a key understanding of the treatment areas and practice in handling the Plasmat® Futura. Our technical department reacts fast and provides an excellent service.

User-friendly and reliable technology with:

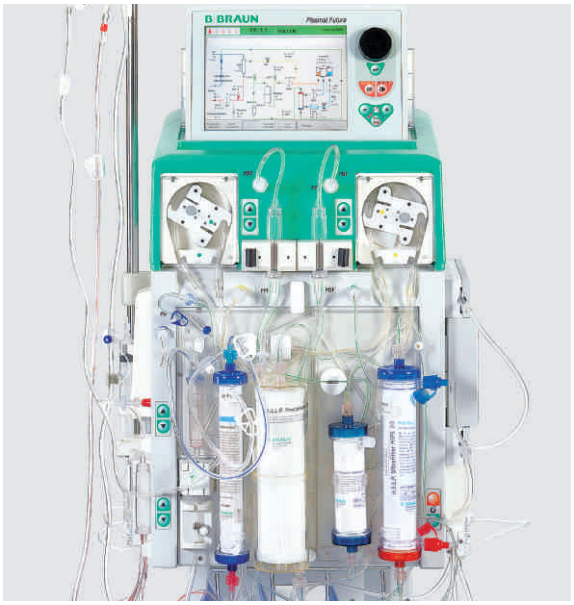
- 4-pump compact system monitor operated, pre-assembled cassette system and balance scales
- Observation monitor with clearly arranged menu structure, a clear display and easily variable treatment parameters, reliable guidance through the treatment steps with a fully developed instruction concept, illustration of extracorporeal circulation using a flow diagram
- Intelligent alarm concept: easy-to-identify alarms using the information in the flow diagram
- Automatic control of plasma separation
- Observation of the quality of plasma separation by a blood leak detector
- Automatic volume control by means of fluid balancing



Making the operation of a complex system simple and reliable

High selectivity is not achieved with simple solution approaches. The design of the H.E.L.P. systems guarantees the patient maximum tolerance of a chronic treatment. B. Braun has succeeded in adapting the system ideally to suit the treatment environment

- Set up with pre-assembled components
- Filling, rinsing and reinfusion take place automatically
- Only disposable items are used throughout the treatment
- The device does not need to be descaled or disinfected
- No main water supply or inverted osmosis required



Plasmat® Futura fully equipped

Consumables

Individual components of the H.E.L.P. set

H.E.L.P. kit

H.E.L.P. acetate buffer,
pH 4.85 reaction buffer
for precipitation

H.E.L.P. heparin
Heparin solution for precipitation,
only in combination with the acetate buffer

H.E.L.P. BicEl. ultrafiltration solution using a dual chamber peel-back seal system, contains basic bicarbonate and acid electrolyte concentrate

H.E.L.P. rinsing solution.
Normal 0.9 % saline solution
for preparing the system

H.E.L.P. reinfusion solution.
Normal 0.9 % saline solution
for return of blood/plasma after
discontinuation of the treatment

Service and consultancy inclusive

Excellent advice and information

Apheresis does not only mean a device and consumables. Apheresis as a treatment area has become more extensive and more demanding.

As a user, you find yourself in a complex and heavily regulated environment.

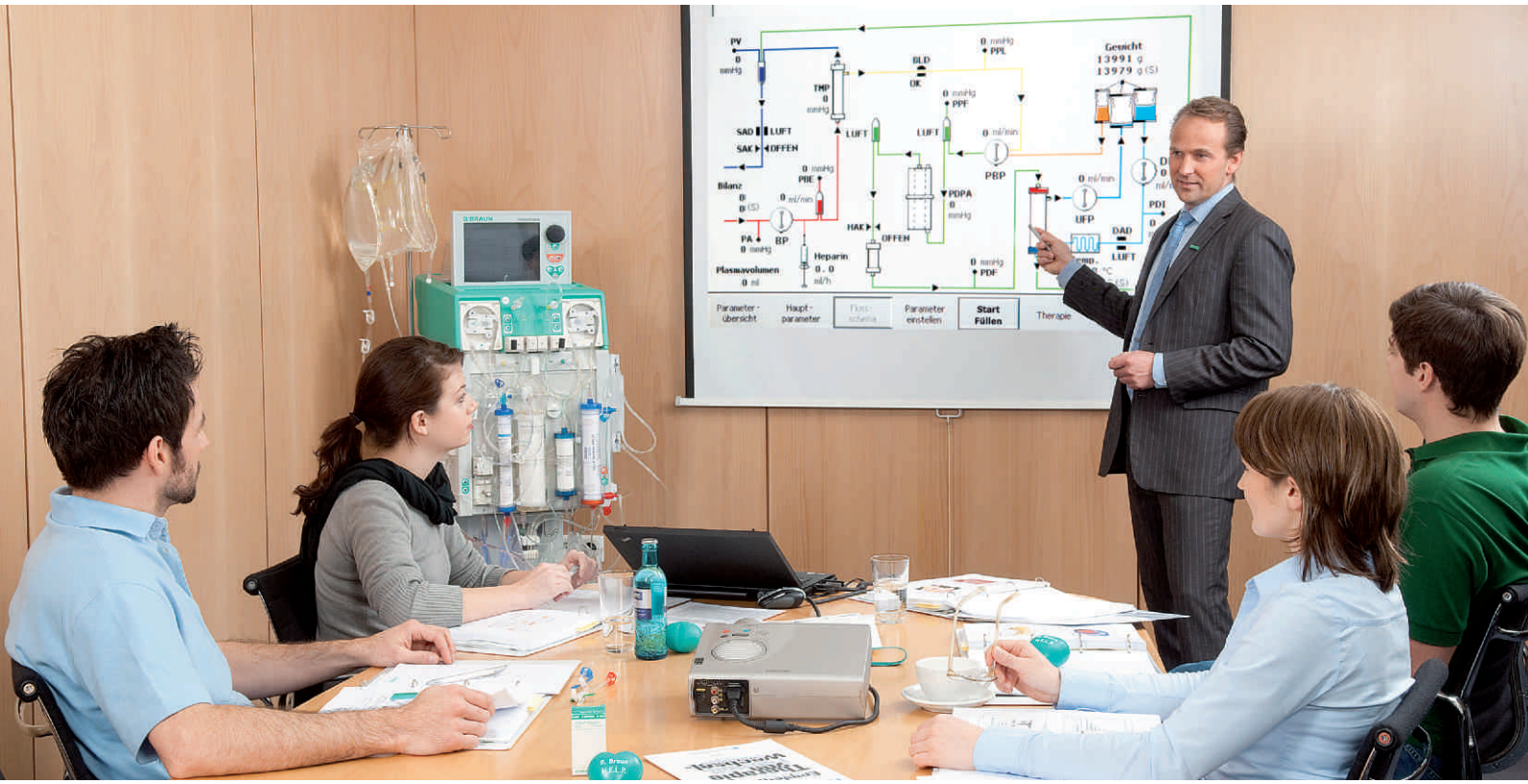
We at B. Braun not only offer you partnership in the technical execution of a treatment. True to our motto "Sharing Expertise", our specially trained product specialists are on hand to offer expert support. We not only provide comprehensive advice on the H.E.L.P. apheresis system itself, but also help you address practical questions regarding your treatment. Our literature service scans the large number of H.E.L.P. publications available to find the one you require. We are happy to help you prepare the content of your presentations. Our publications from the "Forum Antragsstellung" ["Application Forum"] offer effective support for any technical questions. We will also endeavour to provide you with pertinent information on rare indications.

Our product specialists are pleased to support nursing staff with questions on performing H.E.L.P. apheresis. That means providing technical details about the Plasmat® Futura application as well as providing advice on customising an apheresis treatment to suit individual patients' circumstances. In close consultation with the competent physicians and nursing staff, we will always try to find the appropriate solution for you.
Thus we offer you a lasting and expert partnership right from the start.

H.E.L.P. – a strong partner with a long tradition

H.E.L.P. – information from a single source. Direct. Valid. Comprehensive

H.E.L.P. training – Relevant. In-depth. Practical



Good training and induction of your employees goes without saying as far as we are concerned

- Our market-recognised efficient training and induction concept enables you to use the H.E.L.P. apheresis quickly and without complications. In this we endeavour to adapt to your requirements with flexibility.
- We offer you comprehensive training in our own training centre, in which participants receive much more than just training in using the H.E.L.P. apheresis. We also provide information about the science behind the individual indications. We will be happy to offer you a stimulating discussion forum to exchange opinions and experiences.
- Naturally, we also advise and train the users of the H.E.L.P. apheresis directly in the centre. Whether you need an introduction or a refresher course: talk to our expert advisors! We are here to help you.
- By individual arrangement, we also offer physicians seminars and further training on the subject of H.E.L.P.

H.E.L.P. technical service – Reliable. Fast. Close to the client

In daily use, all B. Braun treatment systems for extracorporeal blood treatment are maintained by highly qualified service technicians. They ensure the stable operation of the Plasmat® Futura and carry out all services, repair work and statutory inspections.

Flexibility, total commitment and the high technical expertise of our service team guarantee you an optimum degree of use of your Plasmat® Futura.

- Our technical service begins with the assembly and commissioning of the Plasmat® Futura.
- Annual services and safety checks by our technicians guarantee you a device that is always ready for use.
- The Plasmat® Futura excels thanks to its great technical stability. Nevertheless, if repair work should become necessary, our technicians endeavour to make your Plasmat operational again within as short a time as possible.
- Advisory services for your nursing staff/in-house technicians also form part of the scope of services.
- Competence, friendliness and client-orientation are recognised characteristics of our employees in the technical department.

H.E.L.P. logistics – Prompt. Structured. Flexible

Our service means client proximity

- Reliability in supplying you with consumables is our top priority.
- Our well-structured logistics department ensures that deliveries of consumables proceed smoothly.
- As a rule, deliveries are made within a short time of receipt of the order (*applies for orders received by 14:00 in Melsungen, variations possible in international markets).
- A closely woven network of logistic partners enables you to receive the delivery reliably, even in far-flung regions of the world.
- Would you like a customised delivery schedule? Talk to us!
- Supply bottleneck? We will try to provide you with the essentials on time.


Moscow
Vilnius
Riga
Tønsberg
Stockholm
Copenhagen
Dublin
Sheffield
Glandorf
Berlin
Poznań
Oss
Melsungen
Brussels
Bad Arolsen
Tuttlingen
Bratislava
Prague
Irvine
Bethlehem
Paris
Maria Enzersdorf
Zagreb
Luzern
Budapest
Milan
Temesvár
Barcelona
Naucalpan
de Juárez
Lisbon
Istanbul
Sabana Grande
Karachi
Mumbai
Colombo
Shanghai
Tokyo
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Singapore
Bogota
Quito
Lima
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Buenos Aires
Santiago de Chile
Johannesburg

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