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Low-density Lipoprotein Apheresis: An Overview

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Abstract: Atherosclerosis with myocardial infarction, stroke, and peripheral cellular disease still maintains its position at the top of morbidity and mortality statistics in industrialized nations. Established risk factors widely accepted are smoking, arterial hypertension, diabetes mellitus, and central obesity. Furthermore, there is a strong correlation between hyperlipidemia and atherosclerosis. The prognosis of patients suffering from severe hyperlipidemia, sometimes combined with elevated lipoprotein (a) (Lp(a)) levels, and coronary heart disease (CHD) refractory to diet and lipid-lowering drugs is poor. For such patients, regular treatment with low-density lipoprotein (LDL) apheresis is the therapeutic option. Today, there are four different LDL apheresis systems available: immunoadsorption, heparin-induced extracorporeal LDL/fibrinogen precipitation, dextran sulfate LDL adsorption and LDL hemoperfusion. Regarding the different LDL apheresis systems used, there is no significant difference with respect to the clinical outcome or concerning total cholesterol, LDL, high-density lipoprotein (HDL), or triglyceride concentrations. With respect to elevated Lp(a) levels, however, the immunoadsorption method seems to be the most effective. In 45 patients (25 women, 20 men) suffering from familial hypercholesterolemia resistant to diet and lipid lowering drugs, low-density lipoprotein (LDL) apheresis was performed over 95.6 ± 44.7 months. Four different systems (Liposorber, 32 of 45, Kaneka, Osaka, Japan; Therasorb, 6 of 45, Baxter, Munich, Germany; Lipopak, 2 of 45, Pocard, Moscow, Russia; and Dali, 5 of 45, Fresenius, St. Wendel, Germany) were used. With all methods, average reductions of 57% for total cholesterol, 55.9% for LDL, 75.8% for lipoprotein (a) (Lp[a]), and 45.9% for triglycerides, and an average increase of 14.3% for HDL were reached. Severe side-effects such as shock or allergic reactions were very rare (0.3%) in all methods. In the course of treatment, an improvement in general well-being and increased performance were experienced by 44 of 45 patients. The present data demonstrate that treatment with LDL apheresis of patients suffering from familial hypercholesterolemia resistant to maximum conservative therapy is very effective and safe even in long-term application.
Key Words: Coronary heart disease—Familial hypercholesterolemia—Immunoadsorption—LDL hemoperfusion—Lipoprotein (a) apheresis—Liposorber system—Low-density lipoprotein apheresis.

Despite substantial progress in diagnostics, drug therapy and cardiosurgical procedures, atherosclerosis with myocardial infarction, stroke, and peripheral vascular disease still maintains its position at the top of morbidity and mortality statistics in industrialized nations (1). Established risk factors widely accepted are smoking, arterial hypertension, diabetes mellitus, and central obesity. There is a strong correlation between hyperlipidemia (HLP) and atherosclerosis. The role of cholesterol-bearing lipoproteins in atherogenesis is well established, and in past years, the mode of interaction of these particles with cells has been elucidated. It is suggested that elevated lipid concentrations in the serum lead to their accumulation in the intima of arteries that results in the development of atherogenic plaques. These alterations seem to be accompanied by changes in vessel tone and endothelial regulation (2–7).

Elevated levels of low-density lipoprotein (LDL) cholesterol increase the risk of the development and progression of coronary heart disease (CHD) (8–11). More recent studies have demonstrated the termination of progression, and even regression, of coronary atherosclerosis as a consequence of lipid-lowering intervention (4,12–15). With the introduction of the HMG-CoA-reductase inhibitors, definitive reductions in serum cholesterol levels could be achieved (17–19); however, there are still some patients whose cholesterol levels cannot adequately be controlled by appropriate diet and maximal drug therapy.

All patients with homozygous familial hypercholesterolemia (FH) and patients with severe heterozygous FH belong to this specific group (20–22).

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Surgical procedures, such as portocaval shunt, ileal bypasses, and liver transplantation, can be used to circumvent the disastrous effects of severe hypercholesterolemia, but these measures are associated with a high morbidity rate (23–26).

Largely as a secondary prevention, lowering of elevated plasma lipoprotein concentrations has been shown to be effective (21,27). Patients suffering from severe FH, however, sometimes combined with elevated lipoprotein (a) (Lp[a]) levels, are often refractory to these therapies. With the introduction of LDL apheresis, all forms of hyperlipidemia that were therapy resistant are now effectively treatable (28–35).

METHODS AND PATIENTS

The possible extracorporeal methods for the elimination of LDL cholesterol are summarized in Table 1. Plasma exchange, first described by DeGennes and first used clinically by Thompson, is commonly used in these patients (36,37). Using plasma exchange implies non-specifically removing all important plasma components. Some years later, cascade filtration was used, by introducing a secondary hollow fiber membrane with another cut off, that enables the separation of LDL cholesterol from the physiological macromolecules (38). In some countries, cascade filtration is still in use. A recent development in this field is the introduction of several LDL apheresis techniques that are far more selective than the plasma exchange and cascade filtration procedures (28–34,49).

The purpose of the second part of this overview was to assess the efficacy of regular long-term treatment with different LDL apheresis methods in primary and secondary prevention of atherosclerosis with its complications of coronary heart disease, stroke and peripheral vascular disease. Furthermore, the clinical utility and the safety of the different LDL apheresis methods were evaluated.

Heparin-induced extracorporeal low-density lipoprotein/fibrinogen precipitation

In 1983, heparin-induced extracorporeal LDL/fibrinogen precipitation (HELP) (Braun, Melsungen, Germany) was reported. Plasma and blood cells are separated by a hollow fiber plasma separator. The plasma is then continuously mixed with a sodium acetate buffer (pH 4.84) containing 100 U/mL heparin. The resulting precipitates are removed by filtration through an 0.45 μm polycarbonate filter, and the excess heparin in the filtrate is adsorbed by a diethylaminoethyl (DEAE) cellulose filter. Finally, physiological pH is restored, and excess fluid is removed by bicarbonate dialysis/ultrafiltration before the treated plasma is mixed with the blood cells from the plasma filter and returned to the patient (39–41).

All treatment procedures were performed with Plasma Secura (Braun, Melsungen, Germany) and were regularly supplied with the necessary sterile disposable filters and tubing systems (31,46). The safety and long-term applicability of the HELP system has been proved in more than 100 000 treatments. Seri-

TABLE 1. *Extracoporeal methods for elimination of low-density liporpotein cholesterol (36,37,38,39,40,41,42,43,44,45)*

Authors	Year	Method	Advantage	Disadvantage
De Gennes (36)	1967	Plasmapheresis	Quick, considerable elimination of pahtologic substances	Unselective, danger of infection, bleeding, sensitivity of human albumin
Thompson et al. (37)	1975	Plasmapheresis	Quick, considerable elimination of pahtologic substances	Unselective, danger of infection, bleeding, sensitivity of human albumin
Agishi et al. (38)	1980	Cascadefiltration	Semiselective	Danger of infection, low effectivness
Stoffel et al. (39)	1981	Immunoadsorption	Selective, effective, regenreation, reusable	Expended technology
Borberg et al. (40)	1983	Immunoadsorption	Selective, effective, regenreation, reusable	Expended technology
Wieland et al. (41)	1983	Heparin-induced LDL precipitation (HELP)	Selective, effective	Expended technology
Nosé et al. (42)	1995	Thermofiltration	Selective, effective	Expended technology, behavior of macromolecules under heat unknown, not available
Bosch et al. (44)	1987	Dextran sulfate LDL adsorption	Selective, effective	Expended technology
Mabuchi et al. (43)	1993	LDL hemoperfusion	Selective, effective, simple technology	Unknown
Otto et al. (45)	2002	LDL hemoperfusion	Selective, effective, simple technology	Unknown

TABLE 2. *Clinical results with HELP LDL apheresis (49)*

Authors	Year	Diagnosis	HELP (Patient: *n*)	Drop out (*n*)	Therapy duration	Side effects	Outcome
Seidel et al. (46)	1991	FH, CHD	51	5	1 years	2.9%	46/51 improved
Bosch et al. (50)	1993	FH, CHD, ESRF	3 (HD)	—	1.5 years	13%	3 improved
Schuff-Werner et al. (31)	1994	FH, CHD	51	12	2 years	2.8%	39/51 improved
Jaeger et al. (47)	1997	FH, CHD, HTX	5/10	—	3.6 years	—	5 improved
Mellwig et al. (51)	1998	FH, CHD	9	—	?	—	8/9 improved
Donner et al. (52)	1999	FH	4/11	—	?	?	4/11 improved
Schettler et al. (53)	2000	FH, CHD	18	—	>6 months	—	18 improved

FH, familial hypercholesterolemia; CHD, coronary heart disease; ESRF, end-stage renal failure; HTX, heart transplantation.

ous complications have never been observed (46,47). The technology of the equipment is expended.

Since 1983, many papers have shown that there is clear clinical evidence that a drastic lowering of LDL concentrations by HELP reduces significantly the rate of total and coronary mortality, as well as the incidence of cardiovascular events in high-risk hypercholesterolemic patients (28,31,41,46,47).

More than 120 000 HELP treatments have been performed, demonstrating successful secondary prevention for patients with familial hypercholesterolemia, coronary artery disease, cardiac bypass, or heart transplantation (48). In Table 2, some clinical results with the HELP system are summarized. More than 83% of the treated patients improved and reached a stable situation.

In 1999, Jaeger et al. published the first clinical results with HELP apheresis in acute cerebral infarction (stroke). These results may also benefit from experiences in myocardial ischemia (48). In the same year, Suckfüll et al. published a randomized study of the clinical utility of LDL apheresis in the treatment of sudden hearings loss (54). Their results suggest that the clinical outcome of the treatment of sudden hearing loss after a single HELP apheresis is superior to the more expensive standard treatment with prednisolone, dextrans, and Pentoxifylline.

Immunoadsorption

Immunoadsorption (Plasmaselect, Teterow, Germany) needs a primary separation system with a hollow fiber membrane or a cell separator. The plasma, separated from the whole blood of the patients, was alternately perfused through one of the two immunoadsorption columns. Before the column was saturated with adsorbed lipoproteins (600–800 mL plasma), the plasma flow was switched to the other column; and while one column was used for adsorption, the off-line column was generated with neutral saline buffer solution, glycine buffer (pH 2.4), and neutral buffer again. The treated plasma was then mixed with the cellular components of the blood and returned to the patient. The entire procedure took 2.5–3 h via a computerized apheresis monitor. After the treatment, the columns were rinsed, and after the same procedure, filled with sterile solution. The immunoadsorption columns can be used for a minimum of 40 treatments. The advantages of immunoadsorption are a high selectivity and effectiveness for adsorption of all apo-B-100-containing lipoproteins and showed a beneficial effect of long-term LDL apheresis on atherosclerotic vascular disease (55). A disadvantage is the expended technology.

Since 1993, special immunoadsorption polyclonal antibody columns (Pocard, Moscow, Russia) containing sepharose bound anti-Lp(a) have been available for the treatment of patients with elevated Lp(a) serum concentrations (56–58).

Dextran sulfate low-density lipoprotein adsorption

In 1987, Mabuchi et al. reported on dextran sulfate LDL adsorption for the first time (43). This LDL apheresis is performed using the Liposorber LA-15 system (Kaneka, Osaka, Japan). The components of the system are a hollow-fiber plasma separator, two LDL adsorption columns, each containing 150 mL of dextran sulfate-cellulose beads, a Liposorber tubing system, and an automated computerized apheresis monitor (Apheresis Unit MA-01). The patient's blood was obtained from either the peripheral veins or an a.v. fistula. Heparin was used as the anticoagulant. The plasma, separated from the whole blood of the patient after passing through the hollow-fiber plasma separator, was alternately perfused through one of the two adsorption columns. Before the column was saturated with adsorbed lipoproteins, the plasma flow was switched to the other column, and while one column was used for adsorption, the off-line column was regenerated (the adsorbed liproteins were detached) with hypertonic sodium chloride solution (4.1% NaCl). The treated plasma was then mixed with the cellular components of the blood and returned to the patient. The apheresis machine automatically performed alternate LDL adsorption and

TABLE 3. *Clinical results with dextran sulfate adsorption (Liposorber system)*

Authors	Year	Diagnosis	Liposorber (Patient: *n*)	Drop out (*n*)	Therapy duration	Side effects	Outcome
Gordon et al. (64)	1992	FH	54	—	12 weeks	—	54 improved
Daida et al. (65)	1994	FH, CHD	66	—	1 years	—	45/66 improved
Thompson et al. (66)	1995	FH, CHD	20	—	2.1 years	0.5%	19/20 improved
Kroon et al. (67)	1996	FH, CHD	21	—	2 years	1.3%	21 improved
Gordon et al. (62)	1997	FH, CHD	45	4	22 weeks	4%	41/45 improved
Bambauer et al. (63)	1997	FH, CHD	120	35	6 years	2.2%	85/120 improved
Mabuchi et al. (68)	1998	FH, CHD	130	—	6 years	—	94/130 improved
Nishimura et al. (69)	1999	FH	30	5	2.3 years	—	4/25 improved

FH, familial hypercholesterolemia; CHD, coronary heart disease; ESRF, end-stage renal failure; HTX, heart transplantation.

regeneration of the off-line column, enabling the continuous elimination of apolipoprotein B (apoB)-containing lipoproteins from the plasma. The entire procedure, which took 2.5–3 h, was controlled by a computerized apheresis machine (43,59–63).

The advantage of the Liposorber system is the selectivity by elimination of all apoB-containing lipoproteins and the high effectiveness. A disadvantage is the expended technology.

With dextran sulfate LDL adsorption (Liposorber system), a safe but aggressive, reliable cholesterol-lowering therapy is possible. More than 60% of the precholesterol values can be eliminated by one treatment with the Liposorber system. The effectiveness has been observed in several long-term investigations (Table 3). In more than 75% of cases, the treated patient improved or reached regression of coronary atherosclerosis. The observed side-effects were between 0.5% and 4% (62,63,66,67). The Liposorber system is safe and effective even in high-risk hypercholesterolemia patients. Although evaluation of the effectiveness of LDL apheresis on coronary arterial lesions has not been fully established yet, evidence is accumulating to show, not only the prevention of the development of coronary heart disease, but also regression by lowering of cholesterol to an optimum level in all untreatable hypercholesterolemia patients.

For over a year, a whole-blood lipoprotein apheresis system (Liposorber D) has been available. The first clinical results from this are very encouraging. The advantage is a good selectivity and effectiveness and a simple technology (45).

Low-density lipoprotein hemoperfusion

Low-density lipoprotein hemoperfusion (direct adsorption of lipoproteins, DALI: Fresenius, St. Wendel, Germany) was first described by Bosch et al. (44) in 1993. The new adsorber, which is compatible with human whole blood, contains polyacrylate in the column. In the DALI system, blood is perfused through the adsorber, which contains 480 mL of polyacrylate-coated polyacrylamide, without regeneration. The column has a capacity of more than 1.5–2.0 blood volumes for effective adsorption of cholesterol, LDL, Lp(a), triglyceride, and so forth. Regeneration is not necessary because the column is used for only one treatment (70–72).

The elimination of LDL cholesterol and Lp(a) from whole blood is achieved by adsorption on to polyacrylate-coated polyacrylamide beads. Polyacrylate, like the LDL receptor, consists of polyanions with negatively charged carboxylate groups. These polyanions interact selectively with the cationic groups in the apoB moiety of LDL and Lp(a). Lipoproteins are immobilized on the adsorber beads by this electrochemical interaction.

Besides lipoproteins, the DALI system also adsorbs the positively charged ions calcium and magnesium. Therefore, the columns have to be prerinsed with 6 L of a priming solution containing these electrolytes. The adsorber is thereby saturated with these cations, thus preventing hypocalcemia and hypomagnesemia (72). The DALI system can be run at three different adsorber sizes (DALI 500, 750, and 1000 mL adsorbers). Special equipment and tubes are available. After passing the adsorber, the blood depleted of all apoB-containing lipoproteins is put back into the patient. In each patient, 1.0–1.5 patient blood volumes were treated per session. The advantages are good selectivity, high effectiveness, and a simple technology.

PATIENTS

Since 1990, a total of 45 patients suffering from severe FH (4 homozygous and 41 heterozygous FH) were treated with LDL apheresis, diet, and lipid lowering drugs for 95.6 ± 44.2 months (range 125 months). Before LDL apheresis, all patients were treated with diet and lipid lowering drugs. At the onset of the trial, 42 of 45 patients were regarded as refractory to con-

TABLE 4. *Main clinical features of the 45 patients studied treated by LDL apheresis*

	n
Coronary heart disease (CHD)	43
Myocardial infarction	42
Percutaneous transluminal angioplasty	42
Stent implantation	8
Coronary artery bypass graft	15
Stroke	11
Claudication	43
Arterial hypertension	43
Type II diabetes mellitus	18

ventional therapy measurements. In 5 of 45 patients, use of lipid lowering drugs was discontinued as a result of severe side-effects (constipation, diarrhea, gastrointestinal discomfort, vomiting, and nausea).

Table 4 shows the characteristics of the 45 patients studied. Before applying LDL apheresis, 43 of 45 patients had CHD with severe angina pectoris symptoms, a history of myocardial infarction, or coronary artery bypass graft (CABG).

Coronary heart disease was diagnosed after a history of myocardial infarction substantiated by electrocardiogram (ECG) or by coronary angiography. Manifestations of peripheral vascular and cerebrovascular disease were taken with a history of transient ischemic attack, stroke, intermittent claudication, rest pain, limb amputation, or arterial surgery. Diabetes mellitus was diagnosed according to the criteria of WHO. Body mass index (BMI) was calculated as weight (in kilograms) per the square of height (in meters).

Treatment modalities

In addition to LDL apheresis, all patients received a diet; 40 of 45 patients received lipid-lowering drugs: fibrates (gemfibrozil 400–10000 mg/day, bezafibrate 200–800 mg/day, and fenofibrate 100–500 mg/day) and HMG-CoA reductase inhibitors (simvastatin 5–40 mg/day, lovastatin 10–80 mg/day, and pravastatin 10–40 mg/day). Four different LDL apheresis systems were used: dextran sulfate adsorption for 30 of 45 (Liposorber), 2 of 45 (Liposorber D, Kaneka), immunoadsorption for 6 of 45 (Therasorb, Baxter), LDL hemoperfusion for 5 of 45 (Dali, Fresenius), and the immunoadsorption system with special anti-Lp(a) columns for 2 of 45 patients (Lipopak, Pocard). In most of the methods, plasma is obtained by a primary separation system.

In all the systems the blood flow was between 30 and 120 mL/min; the perfusion flux was between 10 and 40 mL/min. Treatment lasted on average 2.9 ± 1.1 h (range 0.5–6.5 h). The treatment volume depended mainly on the quality of vascular access. The median was 4.8 L/session (between 0.5 and 0.7 L/session). Anticoagulation was effected using nonfractionated heparin in 30 of 40 patients (4.002 ± 2.096 IU; range 2.000–8.000 IU) and low molecular heparin in 6 of 40 patients (2.010 ± 801 IU; range 2.000–3.000 IU). In 4 of 45 patients treated with the DALI system, acid citrate dextrose-A in a concentration of 1:20/1:40 mL was used.

Serum samples were taken preapheresis and postapheresis. The time-averaged lipid lowering is the mean value over the time between aphereses. According to these findings, the interval values (mean of value pre- and post-LDL apheresis) were used for evaluation. To maintain the time-averaged lipoprotein levels at a desirable level according to the guidelines recommended by the European Atherosclerosis Society (73), LDL apheresis must be repeated between once per week and/or every 3–4 weeks. On average, there were 32.8 ± 12.5 (range 13–61) LDL aphereses per patient per year. Lipid concentrations reached during the study period were compared with long-term average values obtained over a period of 14.3 ± 12.1 (range 2–48) months before the trial.

Clinical outcome

During the trial, an improvement in general well-being and increased performances were experienced in 43 of 44 patients. On average, increased performance was reached 2–4 months after the beginning of LDL apheresis. At the start of the treatment, 43 of 45 patients were suffering from CHD and intermittently from angina symptoms. The mean reduction of the lipoproteins are shown in Table 5 and was between 45.9% for triglycerides, 55.9% for LDL, 57% for total cholesterol and 75.8% for Lp(a).

Presently, 41 of 45 patients are free of symptoms. A reduction of 60 to 100% of nitrate medication was observed in 38 of 43 patients who received this therapy at the beginning of the trial. In the course of the trial, one female patient died of an acute myocardial infarction after a treatment period of 16 months, 3 weeks after the last LDL apheresis. In the other subjects, no further cardiac complaints, strokes, or symptoms of peripheral vascular disease were manifested and no CABG was done, even after long-term treatment.

Percutaneous transluminal angioplasties were performed in only 18 of 45 patients during the LDL apheresis to improve the effectiveness of the treatment.

TABLE 5. *Lipoproteins (mg/dL) in 45 patients (*N *= 4330 LDL apheresis treatments)*

Lipoprotein	Low-density lipoprotein apheresis		Mean percentage changes (%)
	Before	After	
Total Cholesterol (mg/dL)	476.5 ± 75.9	204.5 ± 54.5	–57.0
LDL (mg/dL)	297.6 ± 72.7	131.3 ± 64.5	–55.9
HDL (mg/dL)	37.8 ± 7.9	43.2 ± 11.9	+14.3
Triglycerides (mg/dL)	517.2 ± 214.9	279.7 ± 153.6	–45.9
Lp(a) (mg/dL	73.5 ± 13.6	17.8 ± 9.8	–75.8
ApoB (mg/dL)	273.5 ± 46.8	160.3 ± 58.5	–41.5
Fibrinogen (mg/dL)	49.9 ± 126.7	324.8 ± 100.8	–34.1

LDL, low-density lipoprotein, HDL, high-density lipoprotein; Lp(a), lipoprotein (a); ApoB, apoplipoprotein B.

Since 1990, a total of 4330 LDL apheresis treatments have been performed in 45 patients. During this period, several adverse events classified as severe have been observed; however, no deaths or life threatening or disabling adverse circumstances have been seen.

Slight side-effects of minor clinical relevance were documented in 10.9% of the LDL aphereses. These side-effects were post-treatment venous bleeding, vomiting, hypoglycemia, and hypotension. Serious but not life-threatening side-effects were observed in 14 LDL aphereses (0.3%). These included hypotensive episodes in five treatments and allergic reactions in nine LDL aphereses. In these cases, LDL apheresis was discontinued, and adverse effects were managed without major problems. Also, there was no difference in the frequency of side-effects among the four different apheresis systems used (Table 6).

It should be noted that a special type of hypotensive reaction caused by the release of bradykinin occurred in patients who had previously received concomitant ACE inhibitor treatment. This was first reported on by Olbricht et al. (74) and followed by similar reports from Kroon et al. (75) and Keller (76).

This hypotensive reaction was sometimes associated with flushing, dyspnea and/or bradycardia. Subsequently, we decided that patients taking ACE inhibitors should not be treated with LDL apheresis.

TABLE 6. *Side-effects of long-term low-density lipoprotein aphereses (*N *= 4330)*

Side-effects	No of patients affected	Frequency	
		(*N*)	(%)
Posttreatment venous bleeding	20	1 50	3.5
Vomiting	10	110	2.5
Hypoglycemia	6	105	2.4
Hypotension	15	96	2.2
Allergic reaction	4	9	0.2
Shock	2	5	0.1
Total	57	475	10.9

DISCUSSION

Numerous epidemiologic and intervention studies have shown a positive correlation between elevated serum lipoprotein levels and the development and progression of atherosclerosis with its complications (in particular CHD and peripheral vascular disease), as yet no causal link has been established (12,16,77). Having exhausted all other conservative treatment possibilities, LDL apheresis has been shown to be very effective in the treatment of severe dyslipoproteinemia. The present reductions of serum lipid concentrations during treatment with different LDL apheresis methods are in agreement with the findings of other trials (28,31,59,63,64,78–81).

Assessing clinical outcome of the patients, there were no differences with respect to the four apheresis methods. All of the systems were safe and showed equivalent clinical efficacy even during long-term treatment, and all patients reported symptomatic improvement in angina, dyspnea, and claudication even after only a few apheresis sessions. It was suggested that immediate reduction of the LDL C concentration with LDL apheresis promptly improves endothelium regulation and induces changes in coronary tone by an increase in endothelial derived relaxing factor (63,82,83). A decrease in plasma viscosity, which is caused by the removal of LDL and fibrinogen, may improve vascular function and perfusion and leads to relief of ischemic symptoms.

A new concept is the whole blood adsorber or LDL hemoperfusion. The results with the first LDL hemoperfusion (DALI-system) are comparable with the other LDL apheresis systems. The first results with the new whole blood adsorber Liposorber D are very encouraging. Further studies must show if the LDL hemoperfusion will be the most effective LDL apheresis in coming years.

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