Lipoprotein apheresis: an update


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In 1967, the first plasmapheresis (discontinuous flow) to treat patients with homozygous familial hypercholesterolemia was performed [1]. In the 1980s and 1990s, several lipoprotein apheresis methods that more specifically eliminate atherogenic LDL and lipoprotein(a) (Lp(a)) were developed [2–9]. In the 1980s, we were working as a lipidologic center and saw patients dying due to severe atherosclerotic diseases. At present, 80 patients are being treated with six different methods at the Apheresis center at the University Hospital Dresden. The effectiveness of these methods with respect to lowering of LDL cholesterol and Lp(a) is somewhat different. The number of patients with high Lp(a) levels and with severe atherosclerotic complications has increased steadily since 2008. Several studies have shown a high effectiveness for apheresis treatment in these patients. In the future, new drugs (e.g., lomitapide, mipomersen or PCSK9 inhibitors) will probably modify the position of apheresis in the therapeutic regimen.

Indications for lipoprotein apheresis

The Gemeinsamer Bundesausschuss (Federal Joint Committee), the highest decision-making body of the joint self-government of physicians, dentists, hospitals and health insurance funds in Germany, published official indications for the use of lipoprotein apheresis with respect to hypercholesterolemia in 2003 [11]. The absolute indication is a homozygous familial hypercholesterolemia that leads to severe arterial lesions as early as childhood. This indication is also recognized in other countries, such as in the USA [12], the UK [13] and Italy [14].

Among the 80 patients presently being treated with apheresis at the Apheresis Center at the University Hospital Dresden (Germany), none suffers from homozygous familial hypercholesterolemia. Of 119 patients who underwent apheresis treatment in Saxony (Germany) in 2010, only one woman had this kind of metabolic disorder [15]. Her brother also shows the same disease, but does not want to be treated with the extracorporeal method.

Since the 1980s, several lipoprotein apheresis methods that eliminate atherogenic lipoproteins (LDL and lipoprotein(a) [Lp(a)]) have been developed. These methods are based on the following principles: precipitation, adsorption and filtration. In Dresden (Germany), we started to perform extracorporeal treatment in 1990; in the 1980s we were working as a lipidologic center and saw patients dying due to severe atherosclerotic diseases. At present, 80 patients are being treated with six different methods at the Apheresis center at the University Hospital Dresden. The effectiveness of these methods with respect to lowering of LDL cholesterol and Lp(a) is somewhat different. The number of patients with high Lp(a) levels and with severe atherosclerotic complications has increased steadily since 2008. Several studies have shown a high effectiveness for apheresis treatment in these patients. In the future, new drugs (e.g., lomitapide, mipomersen or PCSK9 inhibitors) will probably modify the position of apheresis in the therapeutic regimen.

KEYWORDS: cardiovascular events HDL cholesterol LDL cholesterol lipoprotein(a) lipoprotein apheresis statins triglycerides

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In the official document, severe hypercholesterolemia is accepted as an indication, although no parameters are provided for classification as ‘severe’ [17]. Genetic testing is not required. The usual interpretation in clinical practice is that severe is not only related to the heterozygous form of familial hypercholesterolemia but to the severity of cardiovascular complications. In this interpretation, the fact that the officially accepted target value has not been reached plays a major role. According to international guidelines [18], the target for LDL cholesterol (LDL-C) should be ≤2.6 mmol/l (100 mg/dl) or ≤1.7 mmol/l (70 mg/dl) in high-risk patients. In other words, this indication implies that lipoprotein apheresis can only be started in patients who already suffered cardiovascular events (e.g., within the framework of secondary prevention). Moreover, the regulations state that dietary and drug therapy should have been performed for at least 1 year, and that the general risk situation of a given patient must be taken into account. In addition to LDL-C, other risk factors are often seen in patients with cardiovascular events: hypertension, diabetes, obesity and positive family history of cardiovascular events [19]. The typical patient referred for apheresis treatment suffers from multiple cardiovascular events and/or interventions, with a background of the presence of several risk factors. Some patients are intolerant to lipid-lowering drugs.

The Federal Joint Committee demands that an apheresis session should decrease the LDL-C level by at least 60% [17]. This goal can easily be obtained with the help of all available lipoprotein apheresis methods.

In 2008, an elevated level of Lp(a) (≥600 mg/l) in association with a documented (either clinically or by imaging techniques) progressing cardiovascular disease was accepted as an indication for lipoprotein apheresis by the Federal Joint Committee in Germany [20]. This indication will be discussed in the section on Lp(a).

In Japan, a peripheral arterial occlusive disease is officially accepted as an indication for lipoprotein apheresis [21], although usually only a limited number of sessions are performed.

**Comparison of available lipoprotein apheresis methods**

The first extracorporeal apheresis method used in homozygous patients since 1967 was plasmapheresis [1]. In some countries, a total plasma exchange is still performed in order to remove LDL particles. However, it has several drawbacks: loss of proteins (usually only albumin is given as replacement); limited efficiency with respect to removal of LDL (~50% reduction rate of LDL-C); HDL cholesterol (HDL-C) is reduced to a high degree; and a high rate of side effects (~12%), but since most patients receive multiple treatments, 40% of patients will experience some reaction during the course of therapy) [22]. Although this therapeutic approach has been used for many years, especially in homozygous patients with familial hypercholesterolemia, it is no longer recommended in the long term. The only acceptable indication for performing an acute total plasma exchange is for patients with a chylomicronemia syndrome with acute pancreatitis, where an effective decrease of excessively elevated triglycerides is urgently needed. In these cases, one plasma exchange is usually enough.

The more specific lipoprotein apheresis methods are based on the following principles: precipitation, adsorption and filtration (Table 1) [2–9]. Table 1 mainly lists those lipoprotein apheresis methods we are using at our center, the Apheresis center at the University Hospital Dresden. Additional methods are:

- Lipoprotein(a) Lipopak® columns (Pocard, Russia): plasma separation by centrifugation, polyclonal monospecific antibodies against human Lp(a) bound to sepharose [23];
- Lipocollect 200/300 (medicollect eK, Germany): cell separator and polyanionic porous silica particles [24];
- Liposorber® LA-15 (Kaneka Corporation, Japan): plasma filter and dextrane sulfate bound to cellulose [25].

For each method, the provider recommends the amount of plasma/whole blood to be processed during the apheresis sessions. Usually, the first treatments are started at a lower volume in order to avoid side effects (e.g., lowering of blood pressure), keeping in mind that new patients are somewhat nervous when they start the extracorporeal treatment.

The limiting factor for the plasma volume to be processed when using the heparin-induced extracorporeal LDL precipitation (HELP) system (B Braun Avitum AG; Melsungen, Germany) is the significant reduction of fibrinogen; thus, only 4000 ml plasma is allowed. With the TheraSorb™ LDL system (Miltenyi Biotec GmbH, Germany), the possible plasma
Table 1. Overview of available lipoprotein apheresis methods.

<table>
<thead>
<tr>
<th>Underlying principle</th>
<th>LA method</th>
<th>Manufacturer</th>
<th>Machine</th>
<th>Essentials</th>
<th>Components</th>
<th>One-way system</th>
<th>Treated volume (ml)</th>
<th>Extracorporeal volume (ml)</th>
<th>Anticoagulation*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precipitation</td>
<td>HELP</td>
<td>B Braun Avitum AG (Melsungen, Germany)</td>
<td>Plasmat Futura</td>
<td>Plasma separation by filter; heparin excess, acidic pH (5.12) by acetate buffer</td>
<td>Plasma filter, precipitation filter, heparin adsorber, ultrafiltration filter</td>
<td>Yes</td>
<td>Not applicable</td>
<td>Up to 4000</td>
<td>188</td>
</tr>
<tr>
<td>Adsorption LDL</td>
<td>TheraSorb™</td>
<td>Miltenyi Biotec GmbH (Bergisch-Gladbach, Germany)</td>
<td>Life 18</td>
<td>Plasma separation by centrifugation; antibodies to apoB coupled to sepharose Polycrylate-coated polycrylamide beads</td>
<td>Disk separator; two columns with sepharose coated with antibodies</td>
<td>Columns can be used at &gt;40 sessions</td>
<td>Not applicable</td>
<td>~4500</td>
<td>80</td>
</tr>
<tr>
<td>DALI</td>
<td>DALI</td>
<td>Fresenius Medical Care GmbH (Bad Homburg, Germany)</td>
<td>Art Universal</td>
<td></td>
<td>One or two columns with beads (DALI 500, DALI 750, DALI 1000 [2 x 500], DALI 1250 [500 + 750])</td>
<td></td>
<td>~9000</td>
<td>Not applicable</td>
<td>DALI 500: 330, DALI 750: 430, DALI 1000: 580, DALI 1250: 680</td>
</tr>
<tr>
<td>Liposorber® D</td>
<td>Liposorber®</td>
<td>Kaneka Corporation (Japan)</td>
<td>DX 21/MA-03</td>
<td>Dextrane sulfate bound to cellulose</td>
<td>One or two columns (DL 75 or DL 100 [2 x 500])</td>
<td>Yes</td>
<td>~8000</td>
<td>Not applicable</td>
<td>DL-75: 494, DL-100: 696</td>
</tr>
<tr>
<td>Liposorber® LA-15</td>
<td>Liposorber®</td>
<td>Kaneka Corporation</td>
<td>MA-03</td>
<td>Dextrane sulfate bound to cellulose</td>
<td>Plasma filter, two adsorber columns</td>
<td></td>
<td>~4000</td>
<td>130/160/185</td>
<td>221/261/291</td>
</tr>
<tr>
<td>Filtration Lipid filtration</td>
<td>Lipid filtration</td>
<td>DIAMED Medizintechnik GmbH (Cologne, Germany)</td>
<td>Octo Nova</td>
<td>Filter separates plasma, filter lipoproteins</td>
<td>Plasma filter, lipoprotein filter</td>
<td>Yes</td>
<td>Not applicable</td>
<td>~4000</td>
<td>215</td>
</tr>
<tr>
<td>MONET</td>
<td>MONET</td>
<td>Fresenius Medical Care GmbH</td>
<td>Art Universal</td>
<td>Filter separates plasma, filter lipoproteins</td>
<td>Plasma filter, lipoprotein filter</td>
<td>Yes</td>
<td>Not applicable</td>
<td>~4000</td>
<td>164</td>
</tr>
</tbody>
</table>

*According to information obtained from the manufacturers.
*Given to the patients.
*TheraSorb LDL anticoagulation can be realized without heparin.
*Depending on the used plasma separator (OP-02/OP-05/OP-08).
volume is not limited, but the duration of a session must be taken into account. For the Direct adsorption of lipoproteins (DALI) system (Fre- senius Medical Care GmbH; Bad Homburg, Germany), 1.6-times the blood volume should be processed; with the Liposorber® D system (Kaneka Corporation; Japan) 1.5–1.8-times the blood volume. Volumes given in Table 1 are those usually reached at our center [26]. However, treatment volumes should clearly be individualized (taking into account the tolerability, blood flow and time of a session) depending on the reached target concentrations [27].

Patients gain weight (~0.5–1 kg) by the end of apheresis sessions (due to initial saline infusions in order to avoid a circulatory collapse when starting the therapy, due to citrate infusion during the session). At the end of the apheresis sessions, the remaining extracorporeal blood/plasma should be returned to the patient. For this purpose, a 0.9% saline solution is infused into the system.

In most cases, it is possible to access the veins simply by puncturing (both arms). Of our 80 patients, less than ten have an arteriovenous fistula.

In the days following an apheresis session, concentrations of LDL-C and Lp(a) increase steadily; this is the reason why the usual recommendation is to perform the apheresis once a week. In critical situations (e.g., a new cardiovascular event shortly after a previous one), two sessions per week may be considered. After several years of apheresis treatment, when LDL-C concentrations before the apheresis sessions are in an optimal range, the treatment interval can be prolonged.

Usually, a lipoprotein apheresis session lasts for 1.5–3 h, depending on the blood flow (~80–120 ml/min), the method used and the target volume of the applied method.

All methods effectively remove apoB-containing lipoproteins (i.e., VLDL, LDL and lipoprotein[a]). HELP and both filtration methods also reduce fibrinogen concentrations, an effect that is usually regarded as positive because it leads to an improvement of the rheological properties of the blood.

### Experience with lipoprotein apheresis

- **Effects on lipid concentrations, on fibrinogen & other parameters**

We compared the efficacy of different lipoprotein apheresis methods with respect to lowering of lipid concentrations [26]. We did not base our calculations of the lipid levels on all available data but only on the last three sessions before we switched to another method, and on the last three sessions before the end of this evaluation. Thus, these results reflect the worst situation with respect to efficacy because the major reason for switching to another method was an insufficient lowering of LDL-C and/or Lp(a). Among 68 patients who attended our center in March 2012, 34 patients were formerly treated by one method only, 17 by two methods, ten by three methods, five by four methods and two by five methods.

The LDL-C levels before apheresis were slightly higher than 3 mmol/l (for all methods); the lowest concentrations of this parameter (mean: <1 mmol/l) after the apheresis sessions were seen when we used the DALI and the Liposorber D systems. The mean reduction rates for these two methods exceeded 70% (Figures 1–3) [26].

The HDL-C concentrations were also somewhat decreased by all methods, but after apheresis, the mean values were not <1 mmol/l. We did not see a significant difference in the HDL-C levels after apheresis between the different lipoprotein apheresis methods. It is quite interesting that some authors have described the removal of atherogenic HDL

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**Table 1.** LDL cholesterol levels before and after lipoprotein apheresis with different methods. All methods effectively reduced the LDL-C levels. LDL-C preapheresis, analysis of variance: not significant. LDL-C postapheresis, analysis of variance: p = 0.000; post hoc tests according to Bonferroni: HELP versus TheraSorb™ LDL: p = 0.049; HELP versus DALI: p = 0.000; HELP versus Liposorber® D: p = 0.000; TheraSorb LDL versus DALI: p = 0.022; DALI versus LF: p = 0.002; LF versus Liposorber D: p = 0.031. The error bars show standard deviations.

DALI: Direct adsorption of lipoproteins; HELP: Heparin-induced extracorporeal LDL precipitation; LDL-C: LDL cholesterol; LF: Lipid filtration; MONET: Membrane filtration optimized novel extracorporeal treatment.
particles by apheresis [28–30]. Lipoprotein apheresis markedly diminished abnormal accelerated CETP-mediated cholesterol ester transfer from HDL to LDL, thus reducing their cholesterol ester content [31]. Lipoprotein apheresis appeared not to impact the intrinsic ability of HDL particles to promote either cellular-free efflux cholesterol from macrophages or to deliver cholesterol esters to hepatic cells [31].

The most expressed reduction rates of fibrinogen were seen with the HELP (~60%) and with the two filtration methods (~50%). With the HELP method, the fibrinogen concentration after apheresis reached approximately 1.5 g/l.

The interval mean levels for LDL-C measured at our center in 2009 and 2010 were 2.63 ± 1.01 mmol/l (maximum: 4.78; minimum: 1.14) [15,32].

Lipoprotein apheresis also exerts pleotropic effects [33,34]:
- Elimination of modified (oxidized) LDL particles [35];
- Influence on the rheologic properties of the blood (mainly via the reduction of fibrinogen and of lipoproteins) [36–38];
- Anti-inflammatory effects (reduction of CRP [39,40]);
- Effects on different cytokines [41–43];
- Effects on lipoprotein-associated phospholipase A2 [44];
- Effects on the positively charged proinflammatory apoE4 [28];
- Effects on shear stress-dependent platelet adhesion [49];
- Effects on FABP4 [46].

Lipoprotein apheresis can induce proliferative activity of circulating endothelial progenitor cells, enhancing vascular repair capacity [47]. These pleotropic effects are supposed to play a role in the antiatherogenic impact of lipoprotein apheresis.

**Effects on macro- & micro-vessels**

It was demonstrated that a HELP treatment improves coronary perfusion (measured by PET) both acutely and in the long term after 9 months of continuous apheresis application [48]. Another group showed an improvement in the microcirculation of the upper limbs under lipoprotein apheresis [49]. After lipoprotein apheresis sessions, the parasympathetic response to cardiovascular stimulation improved and sympathetic outflow to peripheral vasculature was reduced [50]. We also found an increase in vasodilation of the arterioles and the venoles of the retina after an apheresis session [51,52].

**Side effects**

Side effects from all lipoprotein apheresis methods are observed in approximately 5% of the sessions [35,53–55]. This is in agreement with our own practice. We mainly saw the following side effects: problems with venous access; transient hypotension, fatigue after the session; danger of bleeding due to the use of heparin/citrate; hypocalcemia especially associated with citrate infusion; iron deficiency mainly due to the regular bloodletting for diagnostic purposes; edema (legs and, in a few cases, in the face); heparin allergy; and bradykinin syndrome (especially when angiotensin-converting enzyme inhibitors have been used in patients who were allocated to methods with a negatively charged surface [DALI and Liposorber D]).

One problem was that we measured extremely elevated international normalized ratios after HELP sessions in patients taking oral anticoagulants [26]. We switched these patients to other lipoprotein apheresis methods.

During our more than 20 years of experience with lipoprotein apheresis, we can confirm that it represents a safe approach to treat high-risk patients.
patients (even those with a certain degree of cardiac insufficiency).

It has already been mentioned that a total plasma exchange should no longer be performed as a chronic treatment for hypercholesterolemia because it will induce a protein loss (with the exception of albumin which is usually replaced). It must also be stated that the so-called ‘specific’ lipoprotein apheresis methods remove some other proteins besides lipoproteins [56]. Total protein levels are acutely reduced by all methods: less than 10% with DALI and Liposorber D, more than 10% with the other methods [Julius U, unpublished data]. In addition to fibrinogen, also albumin, immunoglobulins and ferritin are eliminated [57].

Effect on cardiovascular events

Several papers describe an effective reduction in the incidence of new cardiovascular events and/or nonprogression or even regression (documented by angiography) when comparing prior years with those under apheresis treatment [10,53,54,58–62]. It must be admitted that the apheresis treatment does not completely prevent new events.

We compared those patients who were on apheresis treatment at our center in 2009 and 2010, and developed new events (n = 20) with those who did not (n = 44) [19]. The following risk factors were found to be associated with events: male gender; coexisting diabetes/glucose intolerance; and an elevation of Lp(a) concentrations. In addition, history of previous cardiovascular events, the efficiency of the lipoprotein apheresis therapy, as judged by the reduction rates of LDL-C and Lp(a), and the duration of the extracorporeal treatment (patients with events had started treatment with lipoprotein apheresis more recently) may play a role. The majority of new events were percutaneous coronary interventions and angina pectoris.

Role of Lp(a) in atherogenesis & impact of lipoprotein apheresis

Elevated Lp(a) is a recognized atherogenic risk factor [63–69]. This association was also shown among the patients of our lipidologic outpatient department [70]. It is likely that the Lp(a) level and not the kringle number is the cause of increased coronary heart disease risk [68]. High levels of Lp(a) can serve as an independent predictor of unfavorable events, including death and nonfatal myocardial infarction during 10 years after coronary artery bypass grafting [71]. A recent meta-analysis suggests that significantly elevated baseline plasma Lp(a) levels are associated with an in-stent stenosis [72].

Mechanistically, elevated Lp(a) levels may either induce a prothrombotic/antifibrinolytic effect, as apoA resembles both plasminogen and plasmin, or may accelerate atherosclerosis because, like LDL, the Lp(a) particle is cholesterol rich, or both mechanisms work [63]. The recently identified binding of oxidized phospholipids to Lp(a) is considered to be one of the possible mechanisms that may explain the pathogenicity of Lp(a) [68].

At present, no drugs influencing Lp(a) levels are available in Europe. The HPS2-THRIVE study with nicotinic acid (and laropiprant) was stopped because of a lack of efficiency on cardiovascular events and because of side effects [73,74]. It is not known whether Lp(a) was measured in this study. The manufacturer took the drug from the market. Nicotinic acid lowers Lp(a) by approximately 30%; there is no study showing that this reduction will lead to a decrease in cardiovascular morbidity or mortality.

Within the framework of our study cited above [26], mean Lp(a) levels before apheresis were between 1000 and 1200 mg/l. All lipoprotein apheresis methods acutely decreased this parameter to less than 400 mg/l in the mean. The lowest Lp(a) concentrations were observed with the Liposorber D method (~200 mg/l). With this method, the mean reduction rate was higher than 80% (Figure 4).
Studies with lipoprotein apheresis in patients with high Lp(a)

In contrast to the situation with drugs, there is strong evidence that lipoprotein apheresis positively affects the incidence of cardiovascular events in patients with isolated elevated Lp(a). The first study showing this was published by Jaeger et al. [75]; our group contributed several patients to this study. When comparing the situation before and during apheresis treatment, an impressive reduction of major adverse coronary events, by approximately 90%, was observed in 120 patients. However, this study has been criticized because of its retrospective character, patient selection, highly variable individual observation periods and statistical problems [76]. This criticism led to the Federal Joint Committee’s demand for proof of the effects of lipoprotein apheresis in patients with high Lp(a) levels within the framework of a prospective randomized study. An apheresis team in Berlin (Germany) designed such a study [76,77], but it was not approved by the ethical review committee; the major problem was the control group.

An Italian group also treated patients with high Lp(a) and angiographically documented coronary heart disease with apheresis [78]. However, no new events or cardiovascular interventions were seen either in this group (21 patients) or a drug-treated control group over an observation period of 1 year. The limitation of this prospective study is its short duration.

The Apheresis Research Institute in Cologne (Germany) organized a multicenter (28 treatment sites throughout Germany; 166 patients) study in patients with high Lp(a) concentrations who started an apheresis treatment between January 2008 and August 2010 [79]. The timeline included a 2-year retrospective (y-2, y-1) and 2-year prospective (y+1, y+2) period, and an additional follow-up period of 2 further years (y+3, y+4). Comparing the 2 years prior to apheresis with the first 2 years of apheresis treatment, the rate of major adverse coronary events was lowered by 78% and the adverse cardiac or vascular events rate by 75.9%. This study avoided several drawbacks of the study published by Jaeger et al. [75].

We published a comparison of the effect of lipoprotein apheresis on the cardiovascular event rates in three groups of patients:

- Isolated elevation of LDL-C (Group 1);
- Combined elevation of both LDL-C and Lp(a) (Group 3) [80].

We also focused on the 2 years before and the first 2 years after the start of apheresis treatment. The following reduction rates for cardiovascular events were observed: group 1: 54%; group 2: 83%; and group 3: 83.5% (statistically significant difference). Thus, it could be clearly demonstrated that the lipoprotein apheresis therapy is even more effective in patients with high Lp(a) levels than in patients with hypercholesterolemia alone.

High Lp(a) levels were among the risk factors that were found in apheresis patients at the Apheresis center at the University Hospital Dresden who suffered from new cardiovascular events (n = 20) in 2009 and 2010, despite the extracorporeal treatment [19].

German cardiologists from Bad Oynhausen (Germany) treated a group of nine patients with selectively elevated Lp(a) with the HELP apheresis method and assessed minimum coronary resistance using PET [81]. They illustrated an influence on endothelial dysfunction in the form of sharply increased minimum coronary resistance. The authors concluded from their observation that Lp(a) seems to exert a similar effect on the vascular wall and vascular function as LDL-C.

Finally, the impact of the Lp(a) Lipopak columns (which specifically eliminate Lp(a) particles and do not decrease LDL-C) on the course of the coronary artery disease was shown in a...
recent publication from Safarova et al. [23]. The authors worked with the following study design: two groups (each 15 patients) on statin therapy, one group additionally treated with Lp(a) apheresis weekly; with blinded quantitative coronary angiography analyses of percentage diameter stenosis; and with minimal lumen diameter performed at baseline and after the 18-month treatment period. The authors concluded that Lp(a) apheresis had a greater efficacy regarding the amount of regressed/stabilized coronary segments than atorvastatin alone in the majority of patients.

In summary, it should be emphasized that Germany is the only country worldwide where the severe atherogenic risk factor, an elevation of Lp(a), is officially accepted as an indication for apheresis. This is especially important because, at present, no prescribable drug has an impact on Lp(a). In the opinion of a lipidologist, the regulations should be modified; not only should progressive atherosclerosis be regarded as an indication but also a severe cardiovascular event at a young age and a positive family history of cardiovascular events in patients with excessively high Lp(a) values.

The literature gives a target level to be reached by apheresis as less than 500 mg/l [62,63]. But according to epidemiological studies, for Lp(a) – as for LDL-C – ‘the lower, the better’ may also be true. The risk for developing atherosclerotic lesions increases when the Lp(a) level is higher than 300 mg/l. In contrast to Kassner et al. who showed a decrease of the Lp(a) concentration before apheresis sessions by approximately 20% after 1 year of apheresis treatment [77], we did not see such a decrease, even in the long term. Thus, we asked our patients with high Lp(a) levels to come to our center weekly.

In 2011, the Federal Joint Committee accepted that no randomized controlled study would be possible in the near future, but requested establishment of a lipoprotein apheresis registry, which was realized in 2012 [12].

**New drugs affecting lipids & the role of lipoprotein apheresis**

There are several new approaches in development that will be used in homozygous – and possibly also in heterozygous – patients with familial hypercholesterolemia: the MTP inhibitor lomitapide (decreasing LDL-C by 50% in addition to a lipid-lowering therapy, including lipoprotein apheresis and Lp(a) by approximately 20%) [34,82]; the apoB synthesis inhibitor mipomersen (decreasing LDL-C by ~25% in addition to a lipid-lowering therapy, also decreasing Lp(a) by ~30%; mipomersen is not licensed in Europe) [34,83]; antibodies against PCSK9 (decreasing LDL-C by more than 60% [with concomitant atorvastatin therapy] and Lp(a) by ~30%) [84]; new CETP inhibitors that, in addition to their effect on HDL-C, also decrease LDL-C and Lp(a) by 36% (anacetrapib and evacetrapib). Lomitapide and mipomersen induce side effects, the antibodies against PCSK9 are relatively well tolerated [85]. All of these drugs will probably not replace the lipoprotein apheresis treatment in homozygous patients, but they may be combined with the extracorporeal treatment in order to guarantee better results [12]. On the other hand, among the patients with the so-called ‘severe’ hypercholesterolemia, many patients will no longer be sent to an apheresis center.

Clearly, liver transplantation and gene therapy of the LDL-receptor deficiency will not replace lipoprotein apheresis in severe familial hypercholesterolemia in the near future [86].

With respect to Lp(a), the published preliminary results do not provide any hint that these new drugs will replace lipoprotein apheresis because the reduction rates are too modest.

**Conclusion**

Several lipoprotein apheresis methods based on different principles are available: precipitation, adsorption and filtration. Compared with a total plasma exchange, these methods are much more specific and usually do not induce protein losses. All methods reduce both LDL-C and Lp(a). A reduction of fibrinogen by some methods is usually regarded as beneficial. Some pleotropic effects have been described that may play a role in the antiatherogenic effect of lipoprotein apheresis. There are several studies showing an impressive reduction in the incidence of new cardiovascular events, although none of these studies fulfills the requirements of evidence-based medicine completely. In the last few years, the role of Lp(a) as a risk factor for the development of cardiovascular diseases has been the focus of attention. A few studies have shown good effectiveness of lipoprotein apheresis with respect to cardiovascular events in patients with high Lp(a) concentrations [23,75,79,80]. However, it must be admitted that the final proof can only be obtained by a randomized controlled study. The results shown so far are especially important because, at present, no lipid-lowering drug to reduce Lp(a) levels is available. New lipid-lowering drugs are either being tested...
## Executive summary

### Indications for lipoprotein apheresis

- The homozygous form of familial hypercholesterolemia – in these patients, the lipoprotein apheresis represents a life-saving therapeutic approach.
- Severe hypercholesterolemia when the target values could not be reached, despite a maximal dietetic and drug therapy over at least 1 year; usually these patients suffered from several cardiovascular events.
- Lipoprotein(a) (Lp(a)) levels ≥600 mg/l, plus progressing atherosclerotic disease documented clinically or by imaging techniques, is an indication for lipoprotein apheresis.
- In Japan, a peripheral arterial occlusive disease is officially accepted as an indication for lipoprotein apheresis.

### Total plasma exchange: effective, but has several drawbacks

- There are three major problems when performing total plasma exchange over years:
  - Protein loss;
  - Loss of protective HDL particles;
  - High rate of side effects.
- The only remaining indication is chylomicronemia syndrome with excessively elevated triglycerides and acute pancreatitis; here, it may be life-saving; one session will usually be sufficient.

### Available lipoprotein apheresis methods

- Available lipoprotein apheresis methods are based on the following principles in order to eliminate atherogenic lipoproteins: precipitation, adhesion and filtration.
- Differences between the lipoprotein apheresis methods relate to: effectiveness of lowering of LDL cholesterol and of Lp(a), reduction of fibrinogen levels, treated plasma/blood volume, extracorporeal plasma/blood volume and anticoagulation.
- Pleotropic effects may play a role in the antiatherogenic effect of lipoprotein apheresis.
- Lipoprotein apheresis improves the circulation in micro- and macro-vessels.
- Side effects (mainly hypotension, danger of bleeding, hypocalcemia and iron deficiency) are seldom seen and are easily treated.

### Effects of lipoprotein apheresis on cardiovascular events

- When compared with the situation before the start of the apheresis treatment, a drastic reduction in the event rate was shown in several studies.
- Despite regular apheresis treatment, new events may occur in high-risk patients; the majority of them are coronary interventions and angina pectoris.

### Lp(a) as a cardiovascular risk factor

- Several epidemic studies clearly showed that an elevation of Lp(a) is an important risk factor that is not dependent on other factors but may provide an additional risk.
- Lp(a) plays a role in patients who develop new cardiovascular events, even though they are treated by apheresis.
- Lp(a) has a negative effect in patients who underwent coronary bypass operations or stent implantations.
- At present, there is no drug available that is officially registered to act on Lp(a); nicotinic acid was withdrawn from the market in Europe after a negative study result.

### Studies with lipoprotein apheresis in patients with high Lp(a)

- In studies using lipoprotein apheresis in patients with high Lp(a) levels, a very good reduction of cardiovascular events was demonstrated (compared with the situation before the start of apheresis treatment).
- A randomized controlled study to prove that effectiveness has not been accepted by the ethics review committee.
- With a specific apheresis method that only acts on Lp(a), an improvement of coronary atherosclerosis was shown.
- In some countries, a registry has been started to document the effectiveness of lipoprotein apheresis in a larger patient population.
- The indication of an elevated Lp(a) for the lipoprotein apheresis therapy is officially accepted and reimbursed only in Germany.
- The target level of Lp(a) to be reached by lipoprotein apheresis should still be better defined.

### New drugs affecting lipid concentrations

- New principles to treat lipid disorders have been developed: inhibition of the synthesis of lipoproteins (lomitapide and mipomersen), antibodies against PCSK9 and new CETP inhibitors.
- Lomitapide (in the USA and in Europe) and mipomersen (in the USA only) have been registered for the treatment of homozygous patients with familial hypercholesterolemia.
- The new drugs may change the position of lipoprotein apheresis within the framework of the treatment of high-risk patients in the future.
- The effectiveness of these new drugs to decrease Lp(a) concentrations is rather limited, and it is likely that this indication for lipoprotein apheresis will remain.
now or have just started to be used in medical practice. Some of them may decrease the need for extracorporeal treatment in the future.

**Future perspective**

In Germany, rough estimations have been performed in an attempt to establish the number of patients who may benefit from a lipoprotein apheresis therapy [15,87]. The real numbers of patients on apheresis are much lower (less than half of those with an indication) [15]. Lipoprotein apheresis represents a time-consuming and expensive therapeutic approach, requiring highly qualified staff [88]. An apheresis center should offer at least two methods in order to have the possibility to individualize treatment [26], and at least five patients should be regularly treated.

Particularly in high-risk patients who suffered from multiple cardiovascular events, lipoprotein apheresis has been shown to be highly effective with respect to the reduction of new end points, and, in this way, appears to save costs. This effectiveness will be further demonstrated with the help of registries that have started in Germany, Italy, Sweden and the UK. It is probable that no randomized controlled studies will be feasible in the future. Patients who are intolerant to the available lipid-lowering drugs or who have excessively high levels of Lp(a) appear to highly benefit from the extracorporeal therapy. Lipoprotein apheresis should not be performed solely on the genetic basis of hypercholesterolemia, but keeping in mind the consequences of this metabolic disorder.

Perhaps, in the future, new approaches (e.g., new parameters and a better understanding of the effect of high Lp(a) levels in individuals) to identify high-risk patients before they suffer from cardiovascular events will allow practitioners to start the apheresis treatment within the framework of primary prevention, although this will hardly be realistic in view of the costs involved and the current lack of hard evidence of benefit.

The new drugs now in the pipeline still have to show whether they are really effective with respect to lowering end points. Promising drugs such as nicotinic acid or dalcetrapib were stopped due to the fact that no positive effect could be demonstrated. Moreover, side effects of the new drugs may be of concern.

Lipoprotein apheresis has proven to be a safe therapeutic measure for more than 30 years. In the future, lipidomics may offer new insights into the impact of lipoprotein apheresis on lipoprotein/lipid subfractions [89,90]. Prospective studies comparing different lipoprotein apheresis methods with respect to their influence on cardiovascular events are urgently needed.

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No writing assistance was utilized in the production of this manuscript.

**References**

Papers of special note have been highlighted as:

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8. Dragar LJ, Julius U, Kraenzle K et al. DALI – the first human whole-blood low-


** Tells the story of the Apheresis Center at the University Hospital Dresden.


** Describes the situation with lipoprotein apheresis in a federal state of Germany for the first time.


** Important international guidelines for the diagnostics and treatment of lipid disorders.


** Reports on the effects of a specific lipoprotein(a) apheresis on coronary arteries.


** Summarizes the Dresden experience in patients treated with several lipoprotein apheresis methods.


** Publishes a formula to calculate interval mean values of lipid concentrations in patients treated with lipoprotein apheresis.


Effect of heparin-induced extracorporeal LDL precipitation apheresis on coronary blood flow shown in patients for the first time.

Effect of heparin-induced extracorporeal LDL precipitation apheresis on coronary blood flow shown in patients for the first time.

Effect of heparin-induced extracorporeal LDL precipitation apheresis on coronary blood flow shown in patients for the first time.

Effect of heparin-induced extracorporeal LDL precipitation apheresis on coronary blood flow shown in patients for the first time.


Prospectively performed and confirmed the high effectiveness of lipoprotein apheresis on the incidence of cardiovascular events in patients with isolated elevation of lipoprotein(a).


