Lipoprotein apheresis to treat elevated lipoprotein(a)

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Abbreviations:
apoB: apolipoprotein B; HDL: high-density lipoprotein; LDL: low-density lipoprotein; VLDL: very low-density lipoprotein; CHD: coronary heart disease; FH, familial hypercholesterolemia; Lp(a): lipoprotein(a); HELP: heparin induced extracorporeal LDL precipitation; DALI: direct adsorption of lipoproteins.

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Abstract

An elevated plasma concentration of lipoprotein(a) (Lp(a)) is an independent risk factor for cardiovascular disease. Life style modification and currently available drugs either fail to effectively lower plasma Lp(a) levels or do not result in clinical benefit. However lipoprotein apheresis is very efficient in decreasing Lp(a) concentrations. A single apheresis session can acutely decrease Lp(a) by approximately 60-75% and weekly or biweekly performed apheresis results in considerably decreased mean interval concentrations (approximately 25-40% reduction). While most apheresis systems (HELP, heparin induced extracorporeal LDL precipitation; DALI, direct adsorption of lipoproteins; Lipoprotein apheresis with dextran-sulfate; Lipid filtration; Immunoabsorption) decrease LDL and Lp(a), Lipopac is specific and only decreases Lp(a). Lp(a) apheresis is expensive and time consuming but associated with very few side effects. Two randomized controlled trials give conflicting consults with respect to the effect on angiographic changes. Retrospective analyses indicate that regular apheresis translates into clinical benefit in patients with elevated Lp(a) but adequate, randomized, controlled trials are lacking.

Key words

Apolipoproteins; dyslipidemia; LDL; lipids; lipoproteins; apheresis; extracorporeal; plasmapheresis;
Introduction

Elevated concentrations of Lp(a) are causally linked to atherosclerotic disease (1-3). Decreasing elevated concentrations is therefore a potential strategy to reduce the risk for cardiovascular diseases. In that context the European Atherosclerosis Society generally recommends the reduction of Lp(a) to less than 50 mg/dL (4). However, unlike other disorders of lipid metabolism, elevations of Lp(a) cannot be influenced by lifestyle modification. Similarly, only very few drugs can significantly lower Lp(a) concentrations (niacin, mipomersen and PCSK9 and CETP inhibitors). Treatment with niacin, however, does not translate into clinical benefit, though subjects in these studies had relatively normal baseline Lp(a) levels (5, 6). PCSK9 inhibition seems to be beneficial, it is however unclear if this is related to the Lp(a) lowering effects (7, 8).

Lp(a) concentrations can be reduced by plasma exchange procedures or more specifically by lipoprotein apheresis. In 1975, such procedures were first described as a treatment option for severe hyperlipoproteinemia (homozygous familial hypercholesterolemia) (9). Since the 1980s, more specific techniques were developed to reduce atherogenic apolipoprotein B (apoB) containing particles such as LDL and Lp(a) (10, 11). Currently 5 techniques are available that eliminate apolipoprotein B (apoB) containing lipoproteins. In addition, there is one technique that is specific for Lp(a).

In this review we will discuss the indication for lipoprotein apheresis focusing on patients with elevated Lp(a), describe the different techniques and review the current evidence regarding the efficacy and the long term effect on cardiovascular disease.
Indication for lipoprotein apheresis

Apheresis for elevated LDL-cholesterol:

Indications for apheresis for elevated LDL-cholesterol vary considerably by country (11). In the USA, lipoprotein apheresis is primarily indicated for patients with homozygous familial hypercholesterolemia (FH). It is also approved in other forms of severe LDL-hypercholesterolemia that persist despite maximal drug therapy (LDL >300 mg/dl without concomitant cardio-vascular disease or >200 mg/dl with concomitant cardiovascular disease) (12). In Germany, apheresis for elevated LDL-cholesterol can be performed in severe hypercholesterolemia, if despite maximal dietary and drug therapy, LDL-cholesterol cannot be reduced sufficiently (documented for 12 months). No specific threshold is given because the overall risk profile of the patient should be considered in evaluating the indication for apheresis. In practical terms, this primarily refers to patients with cardio-vascular disease whose LDL-cholesterol remains above 130 mg/dl (variable threshold!) despite maximal possible drug therapy. Other countries have less specific recommendations with respect to apheresis for elevated LDL-cholesterol (11, 13, 14). Generally, homozygous FH is widely recognized as an indication while other forms of LDL-hypercholesterolemia are not.

In Germany, it is estimated that between 2000-2500 subjects are currently being treated with lipoprotein apheresis. Approximately 1000 of them are treated for elevated LDL-cholesterol only. Of the remaining 1000-1500 subjects, approximately half are treated for elevated Lp(a) only while the other half are treated for combined elevations of LDL and Lp(a). Although no exact data are available, the availability of PCSK9 antibodies will most likely decrease the number of patients being treated for elevated LDL-cholesterol only very significantly (by 80-90%?). In addition, some patients treated with apheresis for elevated Lp(a) and LDL-cholesterol will also receive PCSK9 antibody therapy in the future.
Apheresis for elevated Lp(a)

Since apheresis systems for LDL-hypercholesterolemia are based on the elimination of apoB containing lipoproteins, they also decrease Lp(a) concentrations to a similar extent as LDL. However, in most countries, lipoprotein apheresis is rarely used to treat patients with isolated increases of Lp(a). In Germany, increased Lp(a) concentrations are considered to be an indication for regular apheresis in certain patients (fig. 1). According to German guidelines, apheresis may be indicated if Lp(a) is > 60 mg/dl in patients with progressive cardiovascular disease despite optimal control of all other risk factors including LDL-cholesterol; progression must be documented clinically and with imaging techniques (15). Although no exact data are available it is estimated that 1000-1500 patients are undergoing regular apheresis for elevated Lp(a); approximately half of them being treated for isolated Lp(a) elevation (thus, with LDL-cholesterol at goal without apheresis), while the other half is treated with apheresis for elevated Lp(a) and LDL-cholesterol.

Although the FDA does not comment on apheresis for elevated Lp(a), there is a recommendation of the National Lipid Association Expert Panel on Familial Hypercholesterolemia to consider apheresis in functional heterozygotes with LDL-C >200 mg/dL (or non-HDL-C >230 mg/dL) and additional risk factors including high Lp(a) >50 mg/dL (16). Furthermore, apheresis for isolated elevated Lp(a) is also used and reimbursed in US on an ad hoc basis but this option is used rarely at present. The HEART-UK criteria for the use of LDL apheresis include patients with progressive coronary artery disease, hypercholesterolemia, and Lp(a) >60 mg/dl in whom LDL cholesterol remains elevated despite drug therapy (13).

Thus, while Germany is the only country where apheresis may be considered for isolated Lp(a) elevation, in other countries elevated Lp(a) is taken into account when making a decision on using apheresis to treat LDL-hypercholesterolemia.
Procedures

Independent of its indication (elevated LDL and/or elevated Lp(a)) lipoprotein apheresis is usually performed on a weekly or biweekly basis. The duration of every treatment varies between 1.5 and 4 hours. All apheresis techniques can be performed by venous approaches only and all require some form of anticoagulation. Due to the extracorporeal circulation, apheresis may result in a drop in blood pressure. In some patients on regular apheresis, iron deficiency and anemia may develop, which may necessitate iron substitution. However, generally speaking all apheresis methods are tolerated well (17). The different principles underlying the different apheresis systems are shown in figure 2.

Heparin-induced extracorporeal LDL-precipitation (H.E.L.P) is a technique that has been used for more than 30 years (18). It is based on the fact that apoB containing lipoproteins (including LDL and Lp(a)) precipitate in acidic conditions (pH=5.12) by forming a complex with a number of other proteins, including CRP and fibrinogen. The simultaneous elimination of fibrinogen can be seen as an advantage (due to its role in acute coronary events) but also as a disadvantage since the reduction in fibrinogen may limit the amount of plasma that can be treated within one session.

Direct absorption of lipoproteins (DALI) was implemented in 1996 and was the first system to be based on whole blood (19). Similar to the apheresis system using dextran-sulfate, the elimination of lipoproteins is based on electrostatic binding of positively charged apoB to negatively charged polyacrylate ions. The contact of plasma with polyacrylate ions leads to the release of bradykinin. Since the angiotensin converting enzyme (ACE) is responsible for inactivation of bradykinin, treatment with ACE-inhibitors is contraindicated. However, angiotensin-1-receptor antagonists can be used.

Apheresis with dextran-sulfate (Kaneka) introduced in 1984 uses the negative electric charge of cellulose-bound dextran-sulfate to eliminate positively charged apoB-100 (20). Thus, apoB-100
containing particles such as LDL, Lp(a) and VLDL are bound to the column and thus eliminated. This system can be used with plasma or whole blood. Rarely allergic reactions occur. This system also leads to a release of bradykinin; therefore, ACE-inhibitors are contraindicated and should be replaced by angiotensin-receptor antagonists (ACE is involved in the inactivation of bradykinin).

**Lipid filtration/membrane differential filtration** (OctoNova, Diamed) is based on a series of filters whose pores are of such size that only LDL, Lp(a) and fibrinogen are held back (21). The remaining plasma components pass the filter without being eliminated. Obviously this method requires separation of plasma from cellular components of blood beforehand. This method is somewhat less specific than the other available methods.

**Immunapheresis** or immunadsorption was one of the first apheresis techniques to be developed (10). It is based on columns in which sheep antibodies against apoB-100 eliminate apoB-100 containing particles such as LDL, IDL and Lp(a). VLDL are largely protected against elimination because the epitopes on apoB interacting with the antibodies are protected by lipids. The length of an individual apheresis session depends on the plasma volume to be treated (usually reflecting LDL-apoB concentrations). Since the mechanism is very specific for apoB-100 containing particles there is no relevant elimination of other plasma components such as HDL and fibrinogen. Therefore, there is no restriction regarding the treated volume.

**Lipopac apheresis** is another form of immunapheresis introduced in 1994 (22). In contrast to immunoadsorption (antibodies against apoB) the antibodies are directed against apo (a) of Lp(a). Plasma is passed through columns loaded with sheep polyclonal monospecific antibodies against human apo(a). This apheresis system only binds and eliminates Lp(a), while other lipoproteins such as LDL, IDL, VLDL and HGDL are not eliminated. Currently this apheresis system is only available for research purposes.
**Effect of lipoprotein apheresis on lipid levels**

The effect of the different apheresis methods on lipid parameters is relatively homogenous (11, 23, 24). LDL and Lp(a) decrease acutely by approximately 60-75% with each apheresis. HELP, DALI, immunoadsorption, dextran-sulfate and Lipopac (very little effect on LDL) are slightly more effective in reducing Lp(a) levels (61-64%) than the less specific cascade filtration system (53%). It should also be noted that with weekly apheresis, pre-apheresis Lp(a) values tend to decrease over time since the rebound of Lp(a) concentration is not sufficient to achieve baseline values within one week. Depending on the selected interval (weekly or biweekly) and baseline Lp(a) concentration mean interval reduction varies between 20% (biweekly apheresis; relatively low baseline values) (25) and 36% (weekly apheresis, high baseline values) (26). Thus despite resulting in the same immediate Lp(a) reduction, biweekly apheresis results in a much lower interval mean reduction. Unpublished data in 15 subjects from our institution using different apheresis system, indicate that Lp(a) is acutely decreased by 76% with a single apheresis, that mean interval reduction on regular apheresis is 25% and that mean interval concentrations are 40% below the baseline values (concentrations before first apheresis) (fig. 3). Triglycerides are also decreased (up to 50%) but rebound quickly. Similarly, HDL-cholesterol can be transiently decreased by 5-10%.

Analyzing the rebound of plasma concentrations following apheresis allows estimating metabolic parameters (27). Lp(a) concentration rebounds somewhat slower following apheresis than LDL-cholesterol indicating that the half-life of Lp(a) is longer than that of LDL particles which is in good agreement with turnover studies indicating that apo(a) may associate with different apoB-100 containing lipoproteins before elimination from plasma (28).

The various apheresis systems also differ in their capacity to eliminate other proteins. All systems acutely decrease CRP, and most systems (except immunoadsorption) decrease coagulation factors and
complement (29, 30). In addition, HELP decreases fibrinogen very effectively. However all of these proteins rebound quickly (usually <24 h following apheresis and the clinical importance of these reductions remains unclear. However, even after many years of treatment there seems to be no specific side effect relating to the elimination of these proteins.
The effect of apheresis on atherosclerosis

The ultimate goal of regular apheresis for elevated Lp(a) is obviously to reduce cardio-vascular events. Although the causal role of Lp(a) in atherosclerosis is well known and although apheresis can significantly reduce elevated Lp(a) concentrations, no adequately controlled and powered trial has been performed to test the hypothesis that apheresis induced reduction in Lp(a) concentration results in clinical benefit. However, there are a number of studies evaluating potential benefit of apheresis for elevated Lp(a) (table 1).

Thompson et al. evaluated whether in patients with heterozygous familial hypercholesterolemia and coronary heart disease (CHD) (n=39) the combination of biweekly apheresis with simvastatin (40 mg/d) is superior to the combination of colestipol (20g/d) with simvastatin (40 mg/d) (25). After 2.1 years there was no significant difference in angiographic changes between the 2 groups. The authors concluded that “decreasing Lp(a) seems to be unnecessary if LDL cholesterol is reduced to 3.4 mmol/l or less”. However, the study did not select patients with elevated Lp(a) and is therefore limited by a low baseline Lp(a) concentration (43 mg/dl) and only a modest Lp(a) reduction with apheresis (mean interval concentration 33 mg/dl) due to the biweekly apheresis interval.

Safarova et al. more recently evaluated whether atorvastatin together with specific Lp(a) apheresis (Lipopac apheresis) reduces CHD progression on coronary angiography compared to atorvastatin alone in patients (n=30) with CHD and elevated Lp(a) (>50 mg/dl) (31). After 18 months, there was significantly more regression and less progression in the patients treated with atorvastatin and apheresis compared to atorvastatin alone. The trial is limited by a small number of subjects and the lack of reporting of clinical events.

Three German studies with partially overlapping patient cohorts evaluated whether the cardio-vascular
event rate is different during the period before initiation of apheresis and during regular apheresis therapy (26, 32, 33).

The first study by Jaeger et al. (32) compared the MACE (major adverse coronary events—list here the components used in this MACE) before and after initiation of lipoprotein apheresis. 120 patients receiving regular apheresis because of elevated Lp(a) (with or without concomitantly elevated LDL-cholesterol) were included in the analysis. The observation time before initiation of apheresis was 5.6±5.8 years while the observation time on apheresis was 5.0±3.6 years. MACE during the two periods were calculated and compared. The annual MACE rate per person was 1.056 before apheresis and 0.144 during apheresis indicating an 86% risk reduction, which was highly significant (p < 0.0001).

The second study by Rosada et al. (33) included 37 subjects who only had isolated Lp(a) elevation and were treated by regular lipoprotein apheresis. A slightly different approach was used as time to event was calculated for the pre-apheresis period and the on-apheresis period. In the pre-apheresis period, the time from the first recorded cardiovascular event until the next event was calculated while in the on-apheresis period the time from initiation of lipoprotein apheresis until the next event was counted. The 1-year event free survival was 38% during the time period before apheresis while it increased to 75% after initiation of apheresis. This corresponds to an approximately 50% risk reduction and again was highly significant (p < 0.0001).

The third analysis by Leebmann et al. (26) used a similar approach as Jaeger et al. however, only including subjects that were treated for isolated Lp(a) elevation. A total of 170 patients were included and compared MACE in the 2 years before initiation of apheresis and in the following 2 years on apheresis. Mean annual event rate (MACE) was 0.41 during the 2 years before initiation of regular lipoprotein apheresis and 0.09 on regular apheresis, again corresponding to a highly significant 78%
risk reduction (p < 0.0001)

Thus, all 3 studies (partially evaluating the same patients) showed a dramatic decrease in event rates after initiation of regular lipoprotein apheresis. Although these data seem to indicate a very impressive risk reduction, the lack of a control group must be acknowledged as a severe limitation.

Since worsening of atherosclerotic disease is one of the prerequisites to start apheresis for elevated Lp(a), recurrent events must be very common in the time period before apheresis is initiated. Thus, the patient cohort is selected for recurrent events in the pre-apheresis period. It is unclear whether the event rate would remain that high for an extended time period (which is assumed in the analyses). Furthermore, multiple events in a single patient are counted separately resulting in another difficulty: if a patient has a single deadly event 3 years after initiating apheresis the calculated prognosis is much better than for a patient having 2 non-fatal events in the same period, while this is obviously not the case.

The problems associated with the evaluation can also be exemplified with the data of the 4S-trial, a simvastatin secondary prevention trial showing a clear benefit (34% risk reduction) for simvastatin compared to placebo (34). In this statin trial, the annual event rate was 2 per subject before randomization (inclusion criteria was 1 event during the last 6 months). During the trial, the annual event rate was 0.052 per subject in the placebo group (28% over 5.4 years) and 0.035 per subject in the simvastatin group (19% over 5.4 years). If a similar approach as used by Jaeger et al. or Leebmann et al. was applied to these data, a 98.3% risk reduction would have been observed in the simvastatin group and a 97.4% risk reduction in the placebo group. Obviously, the true effect of simvastatin can only be estimated on the basis of a comparison with a control group. Similarly, in any primary prevention statin trial, the event rate will be zero before randomization and will be higher than zero during the trial (in both groups: statin and comparator). Again, the effect of an intervention can only be estimated with the
use of an appropriate control group. These examples highlight the difficulties of interpreting the data shown in the 3 publications.

While it is very likely that Lp(a) reduction by apheresis reduces event rates, the magnitude of the benefit is unclear and cannot be deduced from pre- and post-apheresis evaluations. To correctly determine the effect of Lp(a) apheresis, a study using an adequate control group is required. Such a study must have a controlled, prospective, randomized study design. Ideally, all included patients should have elevated Lp(a) as their only remaining risk factor. While the intervention group should receive weekly or bi-weekly apheresis, the control group should receive standard care (continued optimal control of all other risk factors). Ideally, a third arm, treated by antisense therapy to apo(a) could be included in such a study (35, 36).

Thus, two randomized controlled trials, each with significant limitations gave conflicting results with respect to whether or not apheresis for elevated Lp(a) results in angiographic benefit. The retrospective analyses are hypothesis generating in that they indicate that regular apheresis for elevated Lp(a) may reduce cardiovascular events. An adequately powered and controlled trial is urgently needed to determine whether regular apheresis for elevated Lp(a) translates into clinical benefit.
The future of apheresis for elevated Lp(a)

The future of apheresis for elevated Lp(a) concentrations is difficult to predict. Antisense therapy to apo(a), which is currently being developed, can reduce Lp(a) concentrations even more profoundly than apheresis (35, 36). On the other hand, although time consuming and costly, apheresis is an extremely safe procedure that has been in use for more than 30 years. It is also unclear whether and to what extent elevated Lp(a) remains a risk factor once LDL-cholesterol is reduced to very low levels for example by combined statin and PCSK9 antibody therapy. Ultimately, these questions must be addressed by outcome trials.
Conclusion

In summary, regular apheresis can decrease Lp(a) concentrations acutely by approximately 60-75%, which translates into significant interval mean reduction (25-40%). The procedures are associated with minimal side effects but are cost and time intensive. Retrospective analyses indicate that regular apheresis translates into clinical benefit but adequate, randomized controlled trials are lacking.
References


Figure legends:

Fig. 1: Path to lipoprotein apheresis in Germany. Lipoprotein apheresis can be indicated because of elevated LDL-cholesterol and/or elevated Lp(a) concentrations.

Fig. 2: Mechanisms underlying different apheresis systems for eliminating LDL and/or Lp(a).

Fig. 3: Lp(a) reduction with regular apheresis (schematic presentation), see text for details.
Table 1: Studies evaluating lipoprotein apheresis on cardiovascular outcome

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Population</th>
<th>Duration</th>
<th>Baseline LDL</th>
<th>Baseline Lp(a)</th>
<th>Lp(a) reduction</th>
<th>Primary endpoint</th>
<th>Finding</th>
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<tbody>
<tr>
<td>Thompson(25)</td>
<td>Randomized,</td>
<td>N=39; 72%</td>
<td>2.1 years</td>
<td>6.5±2.0</td>
<td>41±15</td>
<td>58%; interval</td>
<td>Angiographic</td>
<td>No significant difference between drug only and apheresis group</td>
<td>Strength: prospective, randomized, controlled; Limitation: Rel. low baseline Lp(a) concentration; apheresis only every 2 weeks;</td>
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<td>Safarova(31)</td>
<td>Randomized,</td>
<td>N=30; 70%</td>
<td>18 months</td>
<td>2.2±0.2</td>
<td>102±37</td>
<td>73%, interval</td>
<td>Angiographic</td>
<td>Significantly (p&lt;0.01) more regression and less progression with apheresis group</td>
<td>Strength: prospective, randomized, controlled; specific Lp(a) elimination; Limitations: small patient</td>
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<td>Study</td>
<td>Design</td>
<td>N</td>
<td>Age (years)</td>
<td>LDL (mmol/l)</td>
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<td>Event Rate Reduction</td>
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<td>Strength</td>
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<td>Jaeger(32)</td>
<td>Retrospective</td>
<td>120</td>
<td>5.6±5.8</td>
<td>3.26±1.27</td>
<td>4.21±1.5</td>
<td>1.056 per patient year</td>
<td>&lt;0.0001</td>
<td>Large number of patients; different apheresis systems</td>
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<td>Analysis of events observed in periods before and after initiation of apheresis vs apheresis</td>
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<td>LDL-c &gt;2.14 μmol/l</td>
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<td>2.68±0.89</td>
<td>1.056 per patient year</td>
<td>&lt;0.0001</td>
<td>No control group; patients in the studies by Jaeger, Leebmann and Rosada overlap</td>
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<td>Leebmann(26)</td>
<td>Retrospective</td>
<td>170</td>
<td>2 years before</td>
<td>2.56±0.98</td>
<td>3.94±1.77</td>
<td>0.41 per patient year</td>
<td>&lt;0.0001</td>
<td>Large number of patients; only patients with elevated Lp(a); different apheresis systems</td>
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<td>Male; progressive CHD</td>
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<td>LDL-c &gt;2 years after</td>
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<td>2.54±0.99</td>
<td>0.41 per patient year</td>
<td>&lt;0.0001</td>
<td>No control group; patients in the studies by Jaeger, Leebmann and Rosada overlap</td>
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<td>Rosada (33)</td>
<td>Retrospective analysis of events observed in periods before and after initiation of apheresis</td>
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<td>N=37; 95% male; progressive CHD despite low LDL-chol; Elevated Lp(a) (&gt;60 mg/dl)</td>
<td>First event vs. event free survival after initiation of apheresis</td>
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<td>Event free survival after first event</td>
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<td>2.18±0.56 mmol/l</td>
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<tr>
<td>68%; interval mean 83±26 mg/dl</td>
<td>1 year event free survival rate</td>
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<tr>
<td>Significant increase in event free survival 38% per year before initiation of apheresis vs. 75% per year after initiation of apheresis</td>
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**Strength:** only patients with elevated Lp(a); different apheresis systems

**Limitations:** no control group; patients in the studies by Jaeger, Leebmann and Rosada overlap
Atherosclerosis + LDL-cholesterol ↑
Maximal drug therapy

LDL-goal not achieved
(+ worsening of atherosclerosis)

Consider Lipoprotein-Apheresis

Atherosclerosis + lipoprotein(a) >60 mg/dl
Optimization of all other RF

worsening of atherosclerosis

Figure 1
<table>
<thead>
<tr>
<th><strong>HELP:</strong> Heparin-induced extracorporal LDL-precipitation</th>
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</thead>
<tbody>
<tr>
<td>precipitation of a complex consisting of heparin, LDL, lipoprotein(a), and fibrinogen at pH 5.12</td>
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</table>

<table>
<thead>
<tr>
<th><strong>DALI:</strong> Direct adsorption of lipoproteins</th>
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<tbody>
<tr>
<td>Electrostatic interaction of negatively charged polyacrylate anions with positively charged apoB</td>
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</table>

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<tr>
<th><strong>Lipoprotein apheresis with dextran sulfate</strong></th>
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</tbody>
</table>

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<tr>
<th><strong>Lipid filtration/membrane differential filtration</strong></th>
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</thead>
<tbody>
<tr>
<td>Series of filters eliminate LDL and lipoprotein(a) from plasma based on size properties</td>
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</tbody>
</table>

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<tr>
<th><strong>Immunoadsorption: Anti-apoB100 antibodies</strong></th>
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<tbody>
<tr>
<td>Plasma is passed through columns containing polyclonal anti-apoB100 antibodies</td>
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<table>
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<tr>
<th><strong>Lipopac: Anti-apoprotein(a) antibodies</strong></th>
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<tbody>
<tr>
<td>Plasma is passed through columns containing polyclonal anti-apo(a) antibodies</td>
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</tbody>
</table>

Figure 2