**Lipoprotein Apheresis**

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**ABSTRACT**

Lipoprotein apheresis involves the physical removal of lipoproteins from the blood and is employed only in patients where lifestyle and pharmacologic treatment is not capable of decreasing lipoproteins to acceptable levels. There are a number of different guidelines for the use of lipoprotein apheresis. In general, apheresis is indicated for patients with homozygous or heterozygous Familial Hypercholesterolemia (FH) and LDL cholesterol levels >300mg/dl, patients with heterozygous FH and high cardiovascular disease risk characteristics with an LDL cholesterol > 200mg/dl, patients with heterozygous FH and cardiovascular disease or diabetes with an LDL cholesterol > 160mg/dl, or patients with progressive cardiovascular disease and Lp(a) concentrations > 60 mg/dl. Lipoproteins may be removed from the circulation by precipitation, adsorption, or filtration. A number of different systems are currently available for lipoprotein apheresis (heparin precipitation, binding to polyacrylate anions or dextran sulfate, filters that remove lipoproteins based on size, and columns containing antibodies to apolipoprotein B or lipoprotein (a)). The effect of these different lipoprotein apheresis methods on LDL cholesterol and lipoprotein (a) (Lp(a)) levels are very similar with LDL cholesterol and LP(a) levels decreasing by 50-75%. Over 8-13 days the LDL cholesterol and Lp(a) levels increase and may return to baseline levels but in some patients the baseline levels are reduced below the starting values. Triglyceride levels decrease by approximately 50% and HDL cholesterol levels may also decrease depending on the method of apheresis. Triglyceride and HDL cholesterol levels return to baseline levels by 24 hours. Lipoprotein apheresis is generally well tolerated. There are no large randomized studies examining the effect of apheresis on cardiovascular events but there are other types of studies demonstrating the benefits of lipoprotein apheresis on atherosclerosis and cardiovascular disease including observational studies in patients with homozygous FH, studies examining the effect of apheresis on the progression of atherosclerosis, and studies comparing rates of cardiovascular events pre-apheresis and during apheresis. While these studies do not definitively demonstrate that lipoprotein apheresis decreases cardiovascular events, the results of these studies coupled with the randomized studies of LDL cholesterol lowering with drugs makes it extremely likely that lowering LDL cholesterol levels with lipoprotein apheresis will reduce the risk of cardiovascular events. Whether lowering Lp(a) levels with lipoprotein apheresis will reduce cardiovascular events is less certain but given the epidemiology data, genetic studies, basic science experiments, and animal experiments it is very likely that lowering elevated Lp(a) will also have beneficial effects on cardiovascular outcomes. Thus, in carefully selected patient’s lipoprotein apheresis is a useful procedure to lower LDL cholesterol and Lp(a) levels thereby reducing the risk of cardiovascular events. Finally, plasmapheresis has been utilized to rapidly decrease plasma triglyceride levels in patients with very high triglyceride levels and pancreatitis.

**INTRODUCTION**

Lipoprotein apheresis involves the physical removal of lipoproteins from the blood and is employed in patients where lifestyle and pharmacologic treatment is not capable of decreasing lipoproteins to acceptable levels ([1-4](#_ENREF_1)). Lipoprotein apheresis is not widely used but in selected patients can have dramatic effects on lipoprotein levels and clinical benefit ([1-4](#_ENREF_1)).

**INDICATIONS**

Lipoprotein apheresis is only recommended after maximal lifestyle and drug treatment fails to achieve acceptable lipoprotein levels. There are a number of guidelines and recommendations for the use of lipoprotein apheresis. In the United States the Food and Drug Administration has approved the use of lipoprotein apheresis for a limited number of patient categories (Table 1).

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| **Table 1. Patients Approved for Lipoprotein Apheresis by the FDA (Kaneka Medical Products Package Information for Liposorber LA 15 system)**  |
| 1. 1) Familial Hypercholesterolemia homozygotes with LDLc > 500mg/dl
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| 1. 2) Familial Hypercholesterolemia heterozygotes with LDL > 300mg/dl
 |
| 1. 3) Familial Hypercholesterolemia heterozygotes with LDL > 160mg/dl with coronary heart disease
 |
| Patients must be on diet and maximally tolerated drug therapy for 6 months  |

In other countries the guidelines are more liberal. For example, in Germany lipoprotein apheresis is accepted for additional indications (Table 2) ([5](#_ENREF_5)).

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| **Table 2. Indications for Lipoprotein Apheresis in Germany** |
| 1. **1) Primary Prevention**: patients suffering from FH with LDL cholesterol > 160 mg/dl and cardiovascular events in close relatives.
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| 1. **2) Secondary Prevention**: patients with progressive cardiovascular events and LDL cholesterol concentrations > 120–130 mg/dl.
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| 1. **3) Lp(a)**: independent of LDL cholesterol concentrations patients with progressive cardiovascular disease and Lp(a) concentrations > 60 mg/dl.
 |
| Initiation of a lipid apheresis treatment should be considered when diet and lipid loweringdrugs are ineffective  |

In Japan lipoprotein apheresis is approved for patients with coronary artery disease and a total cholesterol level > 250mg/dl ([6](#_ENREF_6)). The National Lipid Association Recommendations are shown in Table 3 ([7](#_ENREF_7)).

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| **Table 3. National Lipid Association Recommendations for Lipoprotein Apheresis** |
| LDL apheresis may be considered for the following patients who, after 6 months, do not have an adequate response to maximum tolerated drug therapy: |
| 1. 1) Functional homozygous FH with LDL-C ≥300 mg/dL (or non-HDL-C ≥330 mg/dL)
 |
| 1. 2) Functional heterozygous FH with LDL-C ≥300 mg/dL (or non-HDL-C ≥330 mg/dL) and 0 to 1 risk factors
 |
| 1. 3) Functional heterozygous FH with LDL-C ≥200 mg/dL (or non-HDL-C ≥230 mg/dL) and high- risk characteristics, such as 2 risk factors or high Lp(a) ≥50 mg/dL using an isoform insensitive assay
 |
| 1. 4) Functional heterozygous FH with LDL-C ≥160 mg/dL (or non-HDL-C ≥190 mg/dL) and very high-risk characteristics (established CHD, other cardiovascular disease, or diabetes)
 |

In general, patients with homozygous Familial Hypercholesterolemia who do not have an adequate response to lipid lowering drugs are candidates for lipoprotein apheresis and this should be initiated as soon as possible. Additionally, apheresis can be considered in patients with elevated cholesterol levels if atherosclerotic vascular disease is present and progressive and if LDL cholesterol treatment goals are not achieved despite maximal drug therapy. The use of lipoprotein apheresis solely for the lowering of Lp(a) is uncertain.

In the United States the widespread use of lipoprotein apheresis is limited by the high expense of this treatment and by the small number of centers that perform this procedure (in the US fewer than 60 centers with approximately 600 patients) ([2](#_ENREF_2)). In contrast, in Germany there are over 350 centers that perform lipoprotein apheresis and the number of patients treated is over 3,000 ([4](#_ENREF_4),[8](#_ENREF_8)).

In pregnant women with homozygous or heterozygous Familial Hypercholesterolemia lipoprotein apheresis when available can be utilized to lower LDL cholesterol levels as the use of many drugs is relatively contraindicated during pregnancy ([9](#_ENREF_9)). In children with homozygous familiar hypercholesterolemia and very high LDL cholesterol levels lipoprotein apheresis treatment can be initiated prior to puberty ([10](#_ENREF_10),[11](#_ENREF_11)).

It is likely that in the future the need for lipoprotein apheresis will be markedly diminished by the recent development of new drugs for lowering LDL cholesterol levels ([12](#_ENREF_12)). For example, in patients with heterozygous FH the use of PCSK9 inhibitors will markedly reduce the need for lipoprotein apheresis ([12](#_ENREF_12)). In patients with heterozygous Familial Hypercholesterolemia on lipoprotein apheresis treatment with a PCSK9 inhibitor resulted in 63% to 77% being able to discontinue lipoprotein apheresis ([12](#_ENREF_12),[13](#_ENREF_13)). In patients with homozygous FH the availability of PCSK9 inhibitors, lomitapide, and evinacumab might also decrease the need for lipoprotein apheresis ([12](#_ENREF_12)). Additionally, in the future drugs that specifically and markedly lower Lp(a) may become available ([14](#_ENREF_14),[15](#_ENREF_15)). Thus, the number of patients that require lipoprotein apheresis should be limited with the majority of patients having homozygous FH.

**LIPOPROTEIN APHERESIS METHODS**

Lipoproteins may be removed from the circulation by precipitation, adsorption, or filtration (Table 4) ([2-4](#_ENREF_2),[8](#_ENREF_8)). A number of different systems are currently available for lipoprotein apheresis (Table 4) ([2-4](#_ENREF_2),[8](#_ENREF_8)).

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| **Table 4. Lipoprotein Apheresis Systems** |
| HELP: Heparin-induced extracorporal LDL precipitation | Based on the precipitation of apolipoprotein B containing lipoproteins in acidic conditions by forming complexes with other proteins |
| DALI: Direct adsorption of lipoproteins | Positively charged apolipoprotein B binds to negatively charged polyacrylate anions |
| Liposorber: Dextran sulfate | Positively charged apolipoprotein B binds to negatively charged dextran sulfate |
| MONET: Lipid filtration | Series of filters eliminate lipoproteins based on size |
| TheraSorb: Apolipoprotein B antibodies | Plasma is passed through columns containing apolipoprotein B antibodies that bind lipoproteins |
| Lipopac: Apoprotein (a) antibodies(this is only used for research purposes) | Plasma is passed through columns containing apoprotein (a) antibodies that bind Lp(a) |

Lipoprotein apheresis is typically carried out on a weekly or biweekly schedule. A typical session is 1.5 – 4 hours. Venous blood is utilized and anticoagulation is required. Some methods utilize plasma (immunoadsorption, filtration, dextran sulfate (Liposorber), HELP) while others utilize whole blood (DALI and dextran sulfate (Liposorber D)) ([2-4](#_ENREF_2),[8](#_ENREF_8)). In the United States HELP precipitation and dextran sulfate adsorption (Liposorber) are approved by the FDA ([2](#_ENREF_2)). A schematic of the Liposorber system is shown in Figure 1.



**Figure 1. Liposorber System (http://www.accessdata.fda.gov/cdrh\_docs/pdf12/H120005b.pdf)**

**EFFECT OF LIPOPROTEIN APHERESIS ON LIPOPROTEINS**

While there are several different lipoprotein apheresis methods (see table 4), the effect of these different methods on plasma lipoprotein levels are similar except for modest differences in their effect on HDL cholesterol levels ([2-4](#_ENREF_2),[16-18](#_ENREF_16)). Soon after lipoprotein apheresis, LDL cholesterol and lipoprotein (a) (Lp(a)) levels are decreased by 50-75% ([2-4](#_ENREF_2),[16](#_ENREF_16)). Over 8-13 days the LDL cholesterol and Lp(a) levels increase such that they may be only modestly decreased or return to baseline prior to the next lipoprotein apheresis session ([2](#_ENREF_2),[4](#_ENREF_4),[19](#_ENREF_19),[20](#_ENREF_20)). Lp(a) levels tend to rebound more slowly than LDL ([2](#_ENREF_2),[4](#_ENREF_4),[20](#_ENREF_20)). After chronic lipoprotein apheresis the pretreatment levels of LDL and Lp(a) in some patients may be reduced by 20 to 40% ([2](#_ENREF_2),[4](#_ENREF_4),[20](#_ENREF_20)). Weekly apheresis is more effective in lowering baseline lipoprotein levels than biweekly apheresis. The concomitant use of drug therapy is beneficial, slowing the rebound in lipoprotein levels, even in patients with homozygous FH ([2](#_ENREF_2),[4](#_ENREF_4),[20](#_ENREF_20)). In a systemic review of children with homozygous familiar hypercholesterolemia lipoprotein apheresis resulted in a 60-70% reduction in LDL cholesterol ([21](#_ENREF_21)).

Triglyceride levels may decrease by 50% with lipoprotein apheresis but the plasma triglyceride levels return to baseline levels by 24 hours ([2](#_ENREF_2),[4](#_ENREF_4)). HDL cholesterol levels also may transiently decrease by 5-20% but return to baseline within 24 hours ([2](#_ENREF_2),[4](#_ENREF_4)). The explanation for the decrease in HDL cholesterol is uncertain, but may be due to hemodilution, activation of hepatic triglyceride lipase, or the decreased activity of LCAT ([2](#_ENREF_2)). Notably the acute decrease in HDL cholesterol is greater than the decrease in apolipoprotein A-I ([2](#_ENREF_2)).

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| **Table 5. Effect of Lipoprotein Apheresis on Plasma Lipid and Lipoprotein Levels** |
| Total cholesterol |  **↓↓↓** |
| LDL cholesterol |  **↓↓↓** |
| Lp(a) |  ↓↓↓ |
| HDL cholesterol |  ↓ |
| Triglycerides |  ↓↓ |

The commonly used lipoprotein apheresis methods are not typically used to remove chylomicrons. Instead in patients with markedly elevated triglycerides and severe pancreatitis plasma exchange may be used to rapidly remove chylomicrons and lower plasma triglyceride levels ([22](#_ENREF_22),[23](#_ENREF_23)).

**TARGET LEVELS OF LIPOPROTEINS DURING LONG TERM LIPOPROTEIN APHERESIS**

The following goals of therapy have been suggested (Table 6) ([20](#_ENREF_20)). It should be recognized that these goals are not based on randomized controlled outcome trials but are suggestions by experts.

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| **Table 6. Lipoprotein Targets During Long Term Apheresis** |
| **Patient Group** | **Lipoprotein** | **Baseline+ (% decrease\*)** | **Interval Mean+ (% decrease\*)** |
| FH Homozygote | LDLc | <332mg/dl (>55) | <254mg/dl (>65) |
| FH Heterozygote | LDLc | --- | <101mg/dl (>60) |
| Increased Lp(a) | Lp(a) | --- | <50mg/dl |

\*Compared with baseline off all lipid lowering treatment

+Baseline levels are immediately before apheresis and interval mean is the level obtained by integrating the area under the post apheresis rebound curve.

**PLEOTROPIC EFFECTS OF LIPOPROTEIN APHERESIS**

In addition to decreasing lipoprotein levels, lipoprotein apheresis has other effects (Table 7) ([1](#_ENREF_1),[2](#_ENREF_2),[24](#_ENREF_24)).

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| **Table 7. Pleotropic Effects of Lipoprotein Apheresis** |
| Decrease in C-reactive protein, SAA, and other inflammatory markers |
| Decrease in fibrinogen and other coagulation factors |
| Decrease in plasminogen and other fibrinolytic proteins |
| Decrease complement |
| Decrease in plasma and blood viscosity |
| Decrease in PCSK9 levels |

It should be noted that the levels of these proteins rapidly return towards normal and the clinical significance of these changes is unknown.

**EFFECT OF LIPOPROTEIN APHERESIS ON ATHEROSCLEROSIS AND CARDIOVASCULAR OUTCOMES**

There are no large randomized outcome studies examining the effect of lipoprotein apheresis on cardiovascular event rates. Performing such a study would be very difficult and given the abundance of evidence that marked hypercholesterolemia causes cardiovascular events randomizing patients with very high levels of LDL cholesterol to a group that is not treated would raise ethical concerns. However, there are a large number of other types of studies that provide insights into the benefits of lipoprotein apheresis on atherosclerosis and cardiovascular events.

**Observational Studies in Patients with Homozygous FH**

In 1985 Thompson and colleagues reported that plasma exchange for a mean of 8.4 years decreased peak serum cholesterol levels by 37% in five patients with homozygous FH and resulted in 5.5 year longer survival than their five respective homozygous siblings ([25](#_ENREF_25)). In a larger group of patients with homozygous FH, Keller also reported that survival was improved in the patients treated with lipoprotein apheresis compared to those treated only with drug therapy ([26](#_ENREF_26)). Additionally, angiographic studies demonstrated that plasma exchange delays the rate of progression of coronary atherosclerosis in homozygotes FH patients ([27](#_ENREF_27)).

**Studies Examining the Effect of Lipoprotein Apheresis on Atherosclerosis**

Several studies have examined the effect of apheresis on atherosclerosis. In 1992 Tatami and colleagues reported that lipoprotein apheresis for greater than one year in 37 patients with hypercholesterolemia (7 homozygote and 25 heterozygote FH patients and 5 undefined patients) had favorable effects on coronary artery stenosis ([28](#_ENREF_28)). As expected, lipoprotein apheresis decreased LDL cholesterol levels. Definite regression was observed in 14 patients, including 4 homozygotes and 10 heterozygotes and regression was observed in patients with severe or mild atherosclerosis. Moreover, the greater the difference in pre and post LDL cholesterol levels the greater the regression in atherosclerosis. Interestingly patients with other risk factors in addition to hypercholesterolemia had less regression.

In 1994 Schuff-Werner and colleagues prospectively determined the efficacy of lipoprotein apheresis in 39 patients with elevated LDL cholesterol levels (286mg/dl) not on statin therapy over a 2 year period ([29](#_ENREF_29)). Lipoprotein apheresis resulted in a rapid decrease in LDL cholesterol levels from 286mg/dl to 121mg/dl one day after apheresis. Moreover, after one and two years of lipoprotein apheresis the baseline LDL cholesterol levels decreased to 203mg/dl and 205mg/dl, respectively. Angiographic studies were obtained in 33 patients before and after 2 years and demonstrated that the mean degree of stenosis of all segments decreased from 32.5% to 30.6% over the 2 years of apheresis treatment (p=0.02). Additionally, regression > 8% was observed in 50/187 (26.7%) segments, 29/187 (15.5%) segments showed progression, and 108/187 (57.8%) segments were stable (< 8% deviation) over 2 years. Finally, the percentage of patients with angina decreased with lipoprotein apheresis.

Waidner and colleagues determined the effect of 3 years of lipoprotein apheresis on coronary artery disease in 32 patients with drug refractory FH ([30](#_ENREF_30)). Apheresis did not significantly improve exercise tolerance. However, quantitative measurement of 111 circumscribed coronary stenoses showed a mean stenosis of 45 +/- 26% at baseline and 43 +/- 22% after apheresis demonstrating no significant improvement with lipoprotein apheresis.

In 1998 Richter and colleagues described the effect of lipoprotein apheresis in 34 patients with coronary heart disease and heterozygous FH not adequately responsive to lipid-lowering drugs ([31](#_ENREF_31)). Baseline LDL cholesterol levels were 269 +/- 62 mg/dl and the calculated-on treatment interval mean LDL cholesterol was 129 +/- 23mg/dl. Coronary angiography revealed regression of lesions in 4 patients (11.8%) and no progression in 19 patients (55.8%).

In a multicenter study Stefanutti et al reported on the effect of lipoprotein apheresis on the progression of coronary artery lesions in 19 patients ([32](#_ENREF_32)). The levels of LDL cholesterol decreased from 130mg/dl pre-apheresis to 41mg/dl post apheresis. Similarly, Lp(a) levels pre-apheresis decreased from 125mg/dl to 34mg/dl post apheresis. Of note, during apheresis both the pre-apheresis LDL cholesterol and Lp(a) levels were lower than baseline values (LDL: 152mg/dl decreasing to 130mg/dl; Lp(a) 172mg/dl decreasing to 125mg/dl). Coronary catheterization revealed that 94.5% of the lesions were stable over 3.1 years.

In 2022 Safarova et al reported the results of lipoprotein apheresis for 10 plus years on carotid intima medial thickness (CIMT) in 10 patients with severe hypercholesterolemia ([33](#_ENREF_33)). Pretreatment LDL cholesterol was 214mg/dL and 40% of the patients had an Lp(a) >60 mg/dL. As expected, LDL cholesterol and Lp(a) levels decreased (over 70% decrease immediately after apheresis). The percentage of patients with CIMT above their "vascular age" decreased from 80% to 30% over the treatment course and the estimated annual rate of change in mean common CIMT was minus 4 µm/year.

In general, these angiographic studies suggest that lipoprotein apheresis has beneficial effects on coronary artery atherosclerosis. It should be recognized that in many of the patients in the studies described above one would expect worsening of coronary atherosclerosis and therefore the lack of progression in these patients suggests benefit. That these studies demonstrate either regression or decreased progression in these high-risk patients indicates lipoprotein apheresis is having beneficial effects on atherosclerosis.

**Studies Comparing Pre-Lipoprotein Apheresis Cardiovascular Event Rates to Cardiovascular Event Rates During Lipoprotein Apheresis**

A number of small studies have compared the rate of cardiovascular events prior to the initiation of lipoprotein apheresis with the rate of cardiovascular events during lipoprotein apheresis treatment. These studies have consistently shown that the rate of cardiovascular events is reduced during apheresis. A larger German Registry study also found evidence supporting a reduction in cardiovascular events during apheresis.

Studies Focusing on LDL Cholesterol

Gordon and colleagues reported the long term effects of lipoprotein apheresis in 49 patients with homozygous (n=10) or heterozygous FH (n=39) ([34](#_ENREF_34)). As expected, there was a 76% decrease in LDL cholesterol levels immediately following apheresis and in patients with homozygous FH there was a progressive decrease in pretreatment LDL cholesterol levels. In patients with heterozygous FH there was no change in pretreatment LDL cholesterol levels. The rate of cardiovascular events during therapy with LDL apheresis and lipid-lowering drugs was 3.5 events per 1,000 patient-months of treatment compared with 6.3 events per 1,000 patient-months for the 5 years before LDL apheresis therapy (P=0.17).

Sachais and colleagues retrospectively studied 34 FH patients treated with biweekly lipoprotein apheresis at the Hospital of the University of Pennsylvania ([35](#_ENREF_35)). As expected, there was a marked reduction of LDL cholesterol level after apheresis and in some but not all patients there was a long-term reduction in their pre-apheresis LDL cholesterol levels. There was a marked decrease in cardiovascular events (3.2-fold decrease) defined as myocardial infarction, stroke, transient ischemic attack or rupture of aortic aneurysm. Similarly, there was also a 20-fold decrease in the need for cardiovascular interventions (coronary artery bypass surgery, carotid endarterectomy, and coronary artery angioplasty or stent placement).

Berent et al in an observational study of 30 patients reported that the incidence of cardiovascular disease 2 years after initiating apheresis compared to the 2 years prior to was reduced by 78% ([36](#_ENREF_36)).

Studies Focusing on LDL Cholesterol and Lp(a)

In a single center study Koziolek and colleagues determined the incidence of major cardiovascular events in 38 patients who were treated during a 20 year period ([37](#_ENREF_37)). LDL cholesterol and Lp(a) were reduced by approximately 60%. Major cardiovascular events were decreased from 7.02% events per patient per year at the start of lipid apheresis to 1.17% during lipid apheresis. Similarly, the rate of myocardial revascularization decreased from 22.8% to 3.8% per patient per year.

A multicenter study by von Dryander and colleagues examined the occurrence of cardiovascular events before apheresis and during apheresis in three groups defined by their lipid patterns at the start of an apheresis treatment: Group 1 (LDL-C ≥ 133mg/dl and Lp(a) ≤ 60 mg/dl; n = 35), Group 2 (LDL-C ≤ 133mg/dl and Lp(a) ≥ 60 mg/dl n = 37), and Group 3 (LDL-C ≥ 133mg/dl and Lp(a) ≥ 60 mg/dl; n = 15) ([38](#_ENREF_38)). LDL cholesterol and Lp(a) levels were decreased by 55-70% by lipoprotein apheresis. Comparisons of the two years before the start of apheresis treatment with the first two years of apheresis treatment revealed the following reductions in the rates of cardiovascular events: Group 1- 54%; Group 2- 83%; Group 3- 83.5%.

In a single center study, Heigl and colleagues examined the effect of lipoprotein apheresis on cardiovascular events in 118 patients with either severe hypercholesterolemia or isolated increases in Lp(a) ([39](#_ENREF_39)). Medium interval between the first cardiovascular event and apheresis treatment was 6.4 ± 5.6 years and the average apheresis treatment period was 6.8 ± 4.9 years. In patients with severe hypercholesterolemia (n=83) baseline LDL cholesterol levels were 176mg/dl and decreased by 67% following apheresis leading to an interval mean value of 120mg/dl. In patients with isolated elevations in Lp(a) (n=35), the baseline Lp(a) was 127mg/dl and decreased by 67% following apheresis leading to an interval mean value of 60mg/dl. After the initiation of lipoprotein apheresis, the annual rate of major cardiovascular events decreased by 80% (p<0.0001). Subgroup analysis showed a 73.7% decrease in patients with severe hypercholesterolemia (p<0.0001) and a 90.4% decrease in patients with isolated elevated Lp(a) levels (p< 0.0001).

Jaeger and colleagues in a longitudinal, multicenter, cohort study determined the effect of lipoprotein apheresis on major coronary events in 120 patients on maximal medical therapy with elevated LDL cholesterol (127mg/dl) and Lp(a) levels (>2.14micromol/l) ([40](#_ENREF_40)). The mean duration of lipid-lowering therapy alone was 5.6 years and that of apheresis was 5.0 years. Median Lp(a) concentration was reduced from 4.00 micromol/l to 1.07 micromol/l (73% decrease) with apheresis treatment (P<0.0001) while LDL cholesterol levels decreased from 127mg/dl to 86mg/dl. Most importantly, major cardiovascular events were reduced by 86% during the lipoprotein apheresis phase (Annual rate 1.056 per patient during the pre-apheresis phase vs. 0.144 per patient during the apheresis phase; p < 0.0001).

In a review of data from the German Lipoprotein Apheresis Registry, the effect of lipoprotein apheresis in 991 patients was described ([41](#_ENREF_41)). As expected, lipoprotein apheresis reduced both LDL cholesterol and Lp(a) levels by greater than 60%. Moreover, there was a 90% decrease in major adverse coronary events as well as a decrease in major adverse non-coronary events by 69 %. An update from the German Lipoprotein Apheresis Registry with 2028 reported similar results ([42](#_ENREF_42)). Similarly, data from the United Kingdom registry reported a reduction in LDL cholesterol and Lp(a) of approximately 40% with a 62.5% reduction in major adverse cardiovascular events between the 2 years prior to, and the first 2 years following introduction of lipoprotein apheresis ([43](#_ENREF_43)).

Studies Focusing on Lp(a)

Rosada and colleagues compared the occurrence of cardiovascular events in 37 patients with elevated Lp(a) levels (112mg/dl) and normal LDL cholesterol levels (84mg/dl) before the initiation of apheresis and during apheresis treatment ([44](#_ENREF_44)). As expected, lipoprotein apheresis resulted in a marked decrease in LDL cholesterol levels (-60%) and Lp(a) levels (-68%). Event-free survival rate after 1 year in the pre-apheresis period was 38% vs. 75% during the apheresis period (P < 0.0001). These results suggest that lowering LDL cholesterol and Lp(a) levels in patients with normal LDL levels and elevated Lp(a) levels by lipoprotein apheresis reduces the number of cardiovascular events.

Leebmann, Roeseler and colleagues carried out a five year prospective observational multicenter study that compared cardiovascular events before and after lipoprotein apheresis in 170 patients with normal LDL cholesterol levels (99mg/dl) and elevated Lp(a) levels (108mg/dl) ([45](#_ENREF_45),[46](#_ENREF_46)). As expected, apheresis reduced Lp(a) levels 68%. Moreover, there was a significant decline of the mean annual cardiovascular event rate from 0.58±0.53 2 years before initiating lipoprotein apheresis to 0.11±0.15 thereafter (P<0.0001). These results further support the hypothesis that lowering Lp(a) levels by apheresis in patients with elevated Lp(a) levels and reasonable LDL cholesterol levels will decrease cardiovascular events.

Grob et al studied 59 patients with elevated Lp(a) levels who were treated with lipoprotein apheresis ([47](#_ENREF_47)). Lp(a) levels were acutely reduced by approximately 70% by apheresis and pre-apheresis Lp(a) levels were decreased by 22.8% compared to baseline. Moreover, cardiovascular events were reduced by approximately 83% during lipoprotein apheresis. Recently, Bigazzi reported in 23 patients with elevated Lp(a) levels and LDL cholesterol levels less than 100mg/dl that lipoprotein apheresis also resulted in a 74% reduction in cardiovascular events during apheresis compared to prior to apheresis ([48](#_ENREF_48)).

Moriarty et al compared cardiovascular events pre and on lipoprotein apheresis in 14 patients with a mean of LDL cholesterol 80mg/dl and Lp(a) level of 138mg/dl pre-lipoprotein apheresis ([49](#_ENREF_49)). On lipoprotein apheresis LDL cholesterol decreased to 29mg/dl and Lp(a) to 51mg/dl. Notably there was a 94% reduction in major adverse cardiovascular events over a mean treatment period of 48 months.

Finally, in a small study Poller and colleagues determined the effect of lipoprotein apheresis in 10 patients with peripheral artery disease who had recently undergone a revascularization procedure and had isolated elevations in Lp(a) (Lp(a) 156mg/dl; LDL cholesterol 85mg/dl) ([50](#_ENREF_50)). After 12 months it was noted that the ankle-brachial-index increased from 0.5 ± 0.2 to 0.9 ± 0.1 (P < 0.001), the mean pain level decreased from 7.0 ± 1.5 to 2.0 ± 0.8 (P < 0.001) as determined using the visual analog scale, and that walking distance increased from 87 ± 60 m to 313 ± 145 m (P < 0.001). Moreover, the frequency of revascularization procedures was decreased (35 revascularizations within the 12 months prior to initiating apheresis vs. 1 revascularization procedure after starting apheresis P<0.001).

While the results of these studies are impressive and demonstrate a consistent reduction in cardiovascular events with the initiation of lipoprotein apheresis in patients with elevations in LDL cholesterol and/or Lp(a) levels it should be recognized that these studies did not include control groups. The absence of a control group is a major limitation. The patients included in these studies were likely selected for treatment with lipoprotein apheresis because they were having progressive cardiovascular events. The decrease in cardiovascular events following the initiation of lipoprotein apheresis could simply represent “regression to the mean” rather than a beneficial effect of apheresis. The inclusion of matched controls who were not treated with lipoprotein apheresis would have increased the significance and the reliability of the above observations. Of course, whether it would be ethical to include such a control group is debatable.

**Controlled Trials**

Studies Focusing on LDL Cholesterol

Koga et al determined the effect of the combination of lipoprotein apheresis plus drug therapy in 2 patients with homozygous FH and 9 patients with heterozygous FH compared to 10 heterozygous FH patients maintained on medication only on carotid intima-media thickness over a greater than 5 year period ([51](#_ENREF_51)). It should be noted that the medication only group was significantly older than the apheresis group. The annual rate of progression of mean maximum intima-media thickness in the common carotid artery was -0.0023+/-0.0246 mm year in heterozygous FH patients treated with LDL apheresis plus drugs while in heterozygote FH patients treated with drugs alone the mean change was +0.0251+/-0.0265 mm year. These results suggest that the long-term treatment with combined lipoprotein apheresis and drugs may delay the progression of the atherosclerotic process and prompt the stabilization of atheromatous plaque in severe FH patients. However, it should be recognized that this was a small non-randomized study and the lipoprotein apheresis plus medication group was not perfectly matched with the medication only group.

Nishimura and colleagues compared angiographic changes after 2.3 years in 25 patients with heterozygous FH treated with lipoprotein apheresis and lipid lowering drugs and 11 patients who declined apheresis and were treated only with drugs ([52](#_ENREF_52)). The apheresis plus drug therapy group was very similar to the lipid lowering drug therapy group. During the trial LDL-cholesterol levels were 140 +/- 34 mg/dl in the apheresis group and 170 +/- 58 mg/dl in the control group (P < 0.05). The mean changes in minimal lumen diameter of lesions were +0.19 +/- 0.30 mm (improved) in the apheresis group (n = 76) and -0.44 +/- 0.40 mm (worsened) in the control group (n = 37) (P < 0.0001). When progression and regression were defined as a change in minimal lumen diameter of +/- 0.67 mm, in the apheresis group, two patients (8%) had progression, 19 (76%) remained unchanged and four (16%) demonstrated regression. In contrast, in the control group seven patients (64%) had progression and four (36%) stayed unchanged. The frequency of regression or no change was greater in the apheresis group than in the control group (P < 0.004). It should be recognized that this was not a randomized study and there may have been subtle differences between the two groups.

Mabuchi and colleagues described the effects of lipoprotein apheresis on coronary artery disease in 43 patients with heterozygous FH treated with cholesterol lowering drug therapy plus apheresis vs. 87 patients with heterozygous FH treated with drug therapy alone ([53](#_ENREF_53)). The patients were not randomized and there were differences in smoking, baseline LDL levels, and percent of patients with coronary artery bypass surgery between the apheresis vs. the drug only group. In the patients treated with apheresis the decrease in LDL cholesterol was 58% (LDL cholesterol on treatment 122mg/dl) while in the drug only group the decrease in LDL cholesterol was 28% (LDL cholesterol on treatment 168mg/dl). Major cardiovascular events including nonfatal myocardial infarction, percutaneous transluminal coronary angioplasty, coronary artery bypass grafting, and death from coronary heart disease were 72% lower in the lipoprotein apheresis group (10%) compared to the drug therapy alone group (36%) (p=0.0088). The lack of randomization and differences in the treatment groups limit the conclusions of this study.

Matsuzaki et al determined the effect of lipoprotein apheresis for one year in 18 patients with heterozygous FH on minimal lumen diameter (MLD) measured by coronary angiogram and plaque area (PA) measured by intravascular ultrasound (IVUS) ([54](#_ENREF_54)). All patients were offered lipoprotein apheresis therapy and 11 patients elected to be treated with medication plus apheresis and 7 patients elected medications alone. The two groups were similar. The apheresis group showed a 34.3% reduction in LDL cholesterol from 213 +/- 25 mg/dl to 140 +/- 27 mg/dl) after one-year. The medication alone group showed no change in LDL cholesterol levels (174mg/dl at baseline and 181mg/dl at one year). Analysis of minimal lumen diameter (MLD) by coronary angiogram revealed an increase in MLD in the apheresis group and a decrease in the medication only group (P=0.008). Analysis of plaque area (PA) by IVUS revealed a decrease in the apheresis group and an increase in the medication only group (p=0.017). Once again, the lack of randomization and the potential for subtle differences in the two groups limit the conclusions of this study.

While the four studies described above were not randomized controlled trials, they nevertheless suggest that lipoprotein apheresis has beneficial effects on the progression of atherosclerosis and the occurrence of cardiovascular events.

In a 2-year randomized trial by Kroon and colleagues 42 men with severe coronary atherosclerosis were randomized to simvastatin 40mg daily (n=21) or simvastatin 40mg daily plus lipoprotein apheresis (n=21) ([55](#_ENREF_55)). Baseline LDL cholesterol levels were approximately 300mg/dl and were reduced by 47% in the simvastatin group and 63% in the simvastatin plus apheresis group. No significant differences in quantitative coronary angiographic end points were observed between the two groups. However, in the simvastatin plus apheresis group bicycle exercise testing revealed a 39% increase in the time to 0.1 mV ST-segment depression and the maximum level of ST depression decreased significantly by 0.07 mV versus no changes in the simvastatin only group. Moreover, regional myocardial perfusion improved in the LDL apheresis group and remained unchanged in the medication group ([56](#_ENREF_56)). Additionally, mean intima-media thickness decreased by 0.05 +/- 0.34 mm in the apheresis group and increased by 0.06 +/- 0.38 mm in the simvastatin-only group (P < 0.001) while the number of patients with hemodynamically significant stenosis in the aorta-tibial vessels decreased from 9 to 7 in the apheresis group and increased from 6 to 13 in the simvastatin alone group (P = 0.002) ([57](#_ENREF_57)). Thus, this study showed that apheresis resulted in functional improvements and a decrease in atherosclerosis in non-coronary vessels. Atherosclerosis in the coronary arteries was not improved by apheresis during this 2-year study. Nevertheless, this randomized trial demonstrates that lipoprotein apheresis has benefits in patients with marked elevations in LDL cholesterol levels.

Studies Focusing on Lp(a)

Ezhov and colleagues studied 30 patients who had coronary heart disease with Lp(a) levels ≥50 mg/dL and LDL cholesterol levels ≤ 100 mg/dL on chronic statin therapy ([58](#_ENREF_58)). Subjects were allocated to treatment with weekly apheresis with an immunoadsorption column specific for Lp(a) ("Lp(a) Lipopak"(®), POCARD Ltd., Russia) plus atorvastatin (n=15) or atorvastatin monotherapy (n=15). As expected in the apheresis group Lp(a) level decreased by an average of 73 ± 12% to a mean of 29 ± 16 mg/dL while there was no significant change in the atorvastatin monotherapy group. Moreover, carotid intima-media thickness (CIMT) did not change in the atorvastatin alone group but in the apheresis group CIMT at 9 and 18 months decreased from baseline by -0.03 ± 0.09 mm (p = 0.05) and -0.07 ± 0.15 mm (p = 0.01), respectively. Additionally, clinical status was improved, with less angina in the apheresis group. This controlled trial demonstrates that lowering Lp(a) by apheresis has beneficial effects on atherosclerosis as determined by measuring CIMT.

In contrast, a study by Thompson and colleagues did not demonstrate a benefit of lowering Lp(a) by lipoprotein apheresis ([59](#_ENREF_59)). In this trial patients with heterozygous FH were randomized to simvastatin 40mg daily plus apheresis (n=20) or simvastatin plus colestipol (n=19). LDL cholesterol levels were slightly lower in the apheresis group (125mg/dl vs. 133mg/dl, p= 0.03) while Lp(a) levels were reduced by 33% (14mg/dl vs. 21mg/dl, p=0.03). After a mean of 2.1 years there were no differences in quantitative coronary angiography between the two groups. The results of this study suggest no benefit to lowering Lp(a) levels. However, it should be noted that in this study the Lp(a) levels were not very high and therefore this study did not examine the effect of lowering Lp(a) levels in patients with elevated levels.

Finally, in a small study by Khan and colleagues randomized 20 patients with refractory angina and elevated Lp(a) >500 mg/L (normal <300 mg/L) and an LDL cholesterol level less than 156mg/dl (4.0 mmol/L), despite optimal lipid lowering drug therapy to lipoprotein apheresis or a sham procedure ([60](#_ENREF_60)). The reported that total carotid wall volume, a marker of atherosclerosis, increased in the sham group but decreased in the lipoprotein apheresis group (P < 0.001 between groups) suggesting that apheresis reduces atherosclerotic burden.

**Summary**

In conclusion, while the studies described above are not perfect and do not definitively demonstrate that lipoprotein apheresis decreases cardiovascular events, the results of the lipoprotein apheresis studies coupled with the randomized studies of LDL cholesterol lowering with statins and other drugs makes it extremely likely that lowering LDL cholesterol levels with lipoprotein apheresis will reduce the risk of cardiovascular events ([12](#_ENREF_12)). Whether lowering Lp(a) levels with lipoprotein apheresis is somewhat less certain, as to date no intervention to lower Lp(a) levels has been shown to reduce events. Nevertheless given the epidemiology data, genetic studies, basic science experiments, and animal experiments it is very likely that lowering elevated Lp(a) will have beneficial effects on cardiovascular outcomes in patients with high Lp(a) levels ([61](#_ENREF_61),[62](#_ENREF_62)).

**OTHER BENEFITS OF LIPOPROTEIN APHERESIS**

Randomized controlled trials have shown that a single lipoprotein apheresis was beneficial in restoring hearing in patients with acute hearing loss ([63](#_ENREF_63),[64](#_ENREF_64)). Additionally, lipoprotein apheresis has been shown to induce remission in approximately 50% of patients with drug-resistant nephrotic syndrome ([1](#_ENREF_1),[65](#_ENREF_65)). The FDA has approved lipoprotein apheresis for new onset focal segmental glomerulosclerosis in pediatric patients who are resistant to standard treatment ([1](#_ENREF_1)). A meta-analysis has also reported benefit in adult patients with focal segmental glomerulosclerosis ([66](#_ENREF_66))

**SIDE EFFECTS AND CONTRAINDICATIONS**

Lipoprotein apheresis in general is well tolerated. During apheresis a decrease in blood pressure may occur in some patients ([2](#_ENREF_2),[3](#_ENREF_3),[8](#_ENREF_8),[16](#_ENREF_16)). Additionally, with long standing apheresis iron deficiency anemia may occur ([67](#_ENREF_67)).

Lipoprotein apheresis using polyacrylate and dextran sulfate columns converts kininogen to bradykinin leading to marked increases in bradykinin levels ([68](#_ENREF_68)). Angiotensin converting enzyme (ACE) inactivates bradykinin and therefore treatment with ACE inhibitors is contraindicated in patients receiving lipoprotein apheresis with polyacrylate or dextran sulfate as the resulting very high levels of bradykinin may lead to severe hypotension and an anaphylactoid reaction ([2](#_ENREF_2),[3](#_ENREF_3),[68](#_ENREF_68),[69](#_ENREF_69)). However, in these patient’s angiotensin receptor blockers can be safely used.

**CONCLUSION**

Lipoprotein apheresis is a well-tolerated procedure that markedly lowers LDL cholesterol and Lp(a) levels in patients who do not obtain acceptable levels with maximal lifestyle and drug therapy. Studies strongly suggest that lipoprotein apheresis will decrease the progression of atherosclerosis and reduce cardiovascular events. Therefore, lipoprotein apheresis is a potential treatment in selected patients with drug resistant elevations in LDL cholesterol and/or Lp(a) levels. Studies have shown that lipoprotein apheresis safely reduces LDL cholesterol levels and xanthomas in children with homozygous Familial Hypercholesterolemia ([21](#_ENREF_21)).

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