REVIEW

LDL-apheresis therapy: current therapeutic practice and potential future use

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Low density lipoprotein (LDL)-apheresis is an approved chronic maintenance therapy for the lowering of plasma cholesterol (LDL reduction >60%) in patients with uncontrolled hypercholesterolemia caused by familial hypercholesterolemia and resistance to pharmacotherapy. Clinical studies have demonstrated its benefit in the reduction of cardiovascular disease. LDL-apheresis can lower other pathological mediators of vascular disease, such as inflammation, hemorrheology, thrombosis and fibrinolysis. The acute and chronic pleiotropic effects of LDL-apheresis on these vascular markers might warrant its use in more diverse settings of vascular disease. This review discusses currently approved LDL-apheresis procedures, the guidelines for their use and current and future therapeutic applications of the technique.

In Western society, more than 50% of all deaths are linked to atherosclerotic diseases [1]. Lowering plasma cholesterol reduces total mortality rates and the National Cholesterol Education Program (NCEP) expert panel recommends reducing plasma levels of low-density lipoprotein cholesterol (LDL-C) as a primary target of lipid-lowering therapy [2]. Recent clinical research demonstrating the benefit of more aggressive lipid reduction for the prevention of cardiovascular disease (CVD) has influenced national guidelines to recommend even lower cholesterol levels [3]. Most patients with CVD, or at risk of developing CVD, can reach their goal for cholesterol reduction by the use of lipid lowering therapy. Despite the effectiveness of these medications, there is still a sizable percentage of patients who, for genetic reasons and/or because of resistance to pharmacotherapy, are unable to reach appropriate levels of plasma cholesterol.

Familial hypercholesterolemia
Familial hypercholesterolemia (FH) is an autosomal dominant disorder resulting in excessive elevations of total cholesterol and LDL [4]. FH is the most common single gene defect, with a frequency of 1 in 500 for heterozygotes and 1 in 1,000,000 for homozygotes. There are an estimated 10 million FH patients worldwide [5]. In addition to elevated cholesterol, the clinical phenotype includes tendon xanthomas and premature CVD. Homozygotes that lack LDL receptors have LDL levels in the range of 200–400 mg/dl and can develop premature CVD. LDL-apheresis was developed for homozygote FH patients and heterozygotes with severe LDL-C elevations unresponsive to medications.

LDL-apheresis
LDL-apheresis was developed in the mid-1980s for patients who required more aggressive management of their plasma cholesterol levels. In 1996, the procedure was approved by the US FDA for use in adults and children with uncontrolled hypercholesterolemia (LDL >200 mg/dl) and CVD or hypercholesterolemia (>300 mg/dl) without CVD. Treatments occur weekly or biweekly depending on the level of plasma cholesterol and severity of CVD. Common LDL-apheresis methods include immunoabsorption (IMA), dextran sulfate adsorption (DSA [Liposorber®] system), heparin extracorporeal LDL precipitation (HELP), direct adsorption of lipoprotein (DALI) and double filtration. Dependent upon the initial levels, apheresis removes LDL in the range of 60–80% (Table 1) [6], and a return to pretreatment levels occurs in approximately 13 days [7]. The volume treated is usually 1–1.5 volumes of either whole blood in DALI (approximately 7 l), or of plasma, using the other procedures (approximately 3–4.5 l). High-density lipoprotein–cholesterol (HDL-C) may be reduced acutely but chronically it remains unchanged or slightly elevated from baseline. Only the dextran sulfate filter (DSA) (Liposorber®) system and HELP are approved in North America and their ability to lower plasma cholesterol is related to the binding of apolipoprotein(apo)B-lipoproteins to...
the (DSA [Liposorber®]) system or precipitation of positively charged apoB-lipoproteins when heparin is added at a low pH (HELP). The DALI system, which treats whole blood, removes LDL by adsorption onto polycrylate-coated beads. IMA removes plasma cholesterol by columns of polyclonal sheep antibodies to human apoB100; double filtration removes lipoproteins by a reduction in pore size in its filter.

HELP & DSA (Liposorber) systems

The two systems approved in the USA are different in their process but generally similar in lipid reduction (Figures 1, 2) [8]. Access occurs through the antecubital veins. Patients may require shunts or fistulas based on poor vascular access. The first step for the HELP (Secura®) process involves filtering whole blood to continuously remove plasma at 20–30 ml/min. The plasma is then mixed with a buffer (pH 4.8) solution containing heparin at a concentration of 100 U/ml. Precipitation of heparin and LDL occurs when the plasma buffer solution reaches approximately pH 5.2. The precipitate is then separated by a second filter as demonstrated in Figure 3. The residual heparin in the LDL-free plasma is adsorbed into another filter. Physiological pH of the plasma and the removal of excess fluid is achieved by dialysis and ultrafiltration. A normal procedure treats approximately 3 l of plasma and at any time only 300–400 ml is ever extracorporal. Albumin, hemoglobin, immunoglobulin, hormones, vitamins, enzymes and electrolytes are not affected significantly by LDL-apheresis, except double filtration, which selectively removes plasma proteins based on size (0.01–0.03 μm) [9].

The DSA (Liposorber) system separates the heparinized plasma with a polysulfone plasma filter. The plasma is exposed to a dextran sulfate cellulose filter within a column that removes the LDL; the device contains two columns. After 500ml of plasma has passed through the first column it is regenerated by a rinsing solution of 5.0% sodium chloride. During the rinsing process, plasma flow is redirected to the second column. Due to the double filtration and rinsing process there is potentially no limit to the amount of LDL adsorbed from the plasma. The twin column process is also found on the immunoadsorption system, but unlike other LDL-apheresis systems the polyclonal sheep antibodies to human apoB100 columns are reusable for at least 40 treatments. Similar to other LDL-apheresis devices, the DSA (Liposorber) system can clog prematurely when treating FH patients who may have severely elevated triglycerides. LDL-apheresis is

### Table 1. Average post-procedure decreases in plasma lipoproteins.

<table>
<thead>
<tr>
<th>Procedure</th>
<th>(n)</th>
<th>Δ%, weighted mean*</th>
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<tbody>
<tr>
<td>IMA</td>
<td>4335</td>
<td>-61.9</td>
</tr>
<tr>
<td>DSA</td>
<td>948</td>
<td>-63.7</td>
</tr>
<tr>
<td>HELP</td>
<td>1581</td>
<td>-59.4</td>
</tr>
<tr>
<td>DALI</td>
<td>32</td>
<td>-77.0</td>
</tr>
</tbody>
</table>

DALI: Direct adsorption of lipoprotein; DSA: Dextran sulphate adsorption; HELP: Heparin extracorporeal LDL precipitation; HDL-C: High-density lipoprotein cholesterol; IMA: Immunoadsorption; LDL-C: Low-density lipoprotein cholesterol; Lp: Lipoprotein.

*Overall mean of the total number of procedures or patients contributing data.

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![Figure 1. Flow diagram of the heparin-induced extracorporeal low-density lipoprotein precipitation (HELP) system.](image-url)
generally not recommended as a treatment for patients with specific hypertriglyceridemia such as familial chylomicronemia.

Further differences identified between the HELP and DSA (Liposorber) procedures involve fibrinogen, bradykinin and portability. HELP removes fibrinogen, a large plasma protein involved in coagulation, inflammation and plasma viscosity in an equal amount to LDL (60–65%). The DSA (Liposorber), as well as the DALI system, lowers fibrinogen levels by only 10-15%. Plasma bradykinin, a potent vasodilator, is produced by the DSA (Liposorber) and DALI procedures through the activation of the intrinsic coagulation pathway [10]. Angiotensin-converting enzyme inhibitors (ACEI) inhibit the breakdown of bradykinin. Because of potential anaphylactoid reactions, ACEI’s are contraindicated for patients using the DSA (Liposorber) or DALI systems or the use of ACEIs needs to be discontinued 48 h before initiating the procedure [11]. HELP does not elevate plasma bradykinin and ACEIs are not contraindicated [12]. Finally, the HELP Secura system requires a reverse osmosis device and external water to dialyze the solution. This process restricts the mobility of HELP. The DSA (Liposorber) system does not require reverse osmosis or external water. In 2001, Braun initiated the HELP Futura system whereby reverse osmosis was replaced with a sterile dialysis solution [13]. The Futura is presently not available in the USA but comparative clinical trials, for FDA approval, will be finished within the year.

Following two decades of use and almost 500,000 treatments, LDL-apheresis has been proven to be an extremely safe procedure. A 5-year post-marketing surveillance study of 622 LDL-apheresis (HELP) patients by Schuff-Werner found a 1–2% incidence of the most common adverse effects, such as failure to achieve vascular access, hypotension and fatigue [14]. LDL-apheresis has been found to be safe when used with children [15] and, although not officially approved for pregnant women, case studies have demonstrated its safety and efficacy during pregnancy [16–18].

Clinical trials

LDL-apheresis was developed for the treatment of atherosclerosis and the prevention of CVD in patients with familial hypercholesterolemia. Due to the limited number of patients who qualify for LDL-apheresis, particularly treatment-naive patients, and the ethical dilemma of not lowering cholesterol appropriately in high-risk patients, there is a lack of randomized double-blinded placebo controlled trials demonstrating...
the significant reduction of CVD morbidity and/or mortality by LDL-apheresis. The Hokuriku study was the largest and longest nonrandomized trial demonstrating the clinical benefits of LDL-apheresis [19]. The trial examined long-term (6 years) safety and efficacy of LDL-apheresis, plus combination lipid-lowering therapy (low-dose statin plus probucol and resin or fibrate) for 43 heterozygous FH patients compared with 87 heterozygous FH patients on a similar combination of lipid-lowering medications. Kaplan-Meier analyses of the coronary events, including nonfatal myocardial infarction, percutaneous transluminal coronary angioplasty, coronary artery bypass grafting and death from coronary heart disease (CHD), found the rate was 72% lower in the LDL-apheresis group (10%) compared with the drug-only group (36%, p = 0.0088).

Observations of other cardiovascular effects related to LDL-apheresis therapy beyond event reduction have included immediate improvement of coronary endothelial function, vasodilation [20], microvascular flow [21] and myocardial perfusion [22]. Long-term use of LDL-apheresis provides information on the procedure’s modification to the vascular wall. Regression of calcified plaque (23%, p <0.01) occurred after 30 months of LDL-apheresis (plus simvastatin 40 mg/day) [23]. Mean carotid intima media thickness (IMT) decreased significantly (0.05 mm) after 24 months with LDL-apheresis (plus simvastatin 40 mg/d) when compared with the simvastatin-only group [24]. Using coronary angiography and intravascular ultrasound, Matsuzaki demonstrated a significant difference in minimal lumen diameter (p = 0.004) and plaque area (p = 0.008) after 1 year in the coronary vessels for LDL-apheresis patients when compared with a control group [25].

Alteration of vascular markers
LDL-apheresis can modify a number of pathological processes associated with CVD (Table 2). Improvements are observed in markers of vascular inflammation such as lipoprotein-associated phospholipase (Lp-PL)A2 [26], fibrinogen, E-selectin, vascular cellular adhesion molecule (VCAM)-1, intercellular adhesion molecule (ICAM)-1 [27], monocyte chemoattractant protein (MCP)-1, lipopolysaccharide binding protein (LBP), matrix metalloproteinase (MMP)-9 and tissue inhibitor of metalloproteinase (TIMP)-1 [30]. C-reactive protein is immediately reduced by up to 65% [31–34] and, following chronic apheresis, the pretreatment levels are lowered by as much as 50% [35].
LDL-apheresis therapy: current therapeutic practice and potential future use – REVIEW

Coagulation factors involved in the prothrombotic pathway are reduced by LDL-apheresis such as tissue factor [28], von Willebrand factor [36], factors V, VII, VIII, XI, XII, soluble CD40 ligand (sCD40L), homocysteine and fibrinogen. Apheresis can also decrease markers that promote the fibrinolytic cascade, including plasminogen, protein S, protein C and antithrombin [37,38]. The reduction of plasma thrombotic and fibrinolytic mediators by apheresis has not resulted in any significant complications of clotting or bleeding. The HELP system primarily affects the extrinsic coagulation system (factors II, VII, IX, X), while the DSA (Liposorber) and DALI systems mainly influence factors of the intrinsic coagulation system (factors IX, X, XI, XII) [39].

Hemorrheology, or resistance to flow, is lowered after LDL-apheresis whereby a single treatment can decrease blood viscosity by 20% [40]. The mechanism for altering blood rheology is related to the improvement of red blood cell aggregation/deformability and plasma viscosity [41,42]. Apheresis' influence on blood viscosity may contribute to the rapid recovery of myocardial blood flow and the minimum coronary resistance seen in patients with coronary artery disease [43].

Increased lipoprotein (Lp)(a) plasma levels are associated with an increased risk for atherosclerosis, myocardial infarction, stroke and restenosis. LDL-apheresis is the only treatment that consistently reduces Lp(a) levels by more than 50% [44]. LDL-apheresis may also increase large buoyant LDL-subfractions [45] and a concomitant decrease of small, dense LDL [46,47]. Apheresis lowers proinflammatory oxidized LDL (Ox-LDL) [48] and increases serum levels of nitric oxide (NO) [49]. This author's unpublished data have demonstrated LDL-apheresis' ability to immediately reduce inflammatory HDL, as measured through HDL's inability to inhibit LDL-induced monocyte chemoattractant activity by 37% [50].

Alternative clinical applications

Peripheral vascular disease

LDL-apheresis can decrease or reverse the progression and symptoms of peripheral vascular disease (PVD). The LDL-apheresis Atherosclerosis Regression Study (LAARS) treated 42 CHD and PVD patients with biweekly apheresis (Liposorber) plus simvastatin 40 mg/day or simvastatin 40 mg/day, for 2 years [24]. Unlike the simvastatin group, apheresis resulted in decreased stenosis of the aorto-tibial tract and decreased mean carotid IMT. Kobayashi and colleagues found that in patients

<table>
<thead>
<tr>
<th>Table 2. Vascular markers changed by LDL-apheresis.</th>
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<tbody>
<tr>
<td>Marker</td>
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<td>-----------------------------------------------</td>
</tr>
<tr>
<td><strong>Pro-inflammatory:</strong></td>
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<tr>
<td>MCP-1</td>
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<tr>
<td>MMP-9</td>
</tr>
<tr>
<td>TIMP-1</td>
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<tr>
<td>ET-1</td>
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<tr>
<td>LBP</td>
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<tr>
<td>Lp-PLA2</td>
</tr>
<tr>
<td>VCAM-1</td>
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<tr>
<td>ICAM-1</td>
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<tr>
<td>E-Selectin</td>
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<tr>
<td>Fibrinogen</td>
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<tr>
<td>Oxidized LDL</td>
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<tr>
<td>CRP</td>
</tr>
<tr>
<td><strong>Vasomotion:</strong></td>
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<tr>
<td>Nitric oxide</td>
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<tr>
<td>Bradykinin</td>
</tr>
<tr>
<td>Endothelin-1</td>
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<tr>
<td>PGI2</td>
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<tr>
<td><strong>Thrombotic:</strong></td>
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<tr>
<td>Tissue factor</td>
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<tr>
<td>von Willebrand factor</td>
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<td>Thrombin</td>
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<td>Factor V</td>
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<tr>
<td>Factor VII</td>
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<td>Factor XI</td>
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<tr>
<td>Factor XII</td>
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<tr>
<td>sCD40L</td>
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<tr>
<td>Homocysteine</td>
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<tr>
<td>Fibrinogen</td>
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<tr>
<td><strong>Fibrinolytic:</strong></td>
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<tr>
<td>Plasminogen</td>
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<tr>
<td>Protein S</td>
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<td>Protein C</td>
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<tr>
<td>Antithrombin</td>
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<tr>
<td><strong>Hemorrheology:</strong></td>
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<tr>
<td>Plasma viscosity</td>
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<tr>
<td>Blood viscosity</td>
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<tr>
<td>RBC aggregation</td>
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<tr>
<td>RBC deformability</td>
</tr>
<tr>
<td>Fibrinogen</td>
</tr>
</tbody>
</table>

CRP: C-reactive protein; ET: Endothelin; ICAM-1: Intercellular adhesion molecule; LBP: Lipopolysaccharide binding protein; LDL: Low-density lipoprotein; Lp-PLA2: Lipoprotein-associated phospholipase A2; MCP-1: Monocyte chemoattractant protein-1; MMP-9: Matrix metalloproteinase-9; PG: Prostaglandin; RBC: Red blood cell sCD40L: Soluble CD40 ligand; TIMP: Tissue inhibitor of metalloproteinase; VCAM-1: Vascular cellular adhesion molecule-1.
with PVD, LDL-apheresis led to an increase in ankle-brachial pressure index (from 0.69 to 0.85) with significant improvements in foot numbness, claudication and foot ulcers of 82, 54 and 14% respectively [29].

**Cerebral vascular disease**

LDL-apheresis trials have examined changes to cerebrovascular function. Pfefferkorn and colleagues measured CO₂ reactivity (a marker of cerebral vasoreactivity) in patients with CAD and hyperlipidemia, and revealed a single treatment of LDL-apheresis significantly improved CO₂ reactivity and plasma viscosity by 14% [51]. Walzland and colleagues used two LDL-apheresis therapies over an 8-day period to treat patients with acute embolic stroke or multi-infarct dementia. Results demonstrated improvements, relative to the control group, (p <0.05) in the Mathew scale and Mini-mental State Examination [52]. LDL-apheresis also produced an immediate and significant reduction of rheological markers (fibrinogen, blood viscosity, plasma viscosity and red cell transit time at 34, 17, 16 and 17%, respectively).

**Cardiac transplantation**

Cardiac transplant (CT) patients can experience complications such as hyperlipidemia, graft versus host disease and hypertension, all of which can accelerate atherosclerosis in comparison with the general population [53]. A study of CT patients with cardiac allograft vasculopathy (CAV) by Park and colleagues found significant increases in mean luminal diameter following LDL-apheresis [54]. Matschke and colleagues found that CT patients with CAV who received LDL-apheresis showed an increase in their intramuscular (anterior tibial) partial pressure (pO₂) by over 150%, values similar to those found in healthy subjects [55]. Jaeger and colleagues confirmed that in CT patients with graft vessel disease on lipid-lowering therapy using weekly HELP can significantly reduce vessel disease when compared with medication alone [56].

**Renal disease**

The rapid development of atherosclerosis in dialysis patients may be linked to the hemodialysis process, which is known to increase Ox-LDL-L-C levels, impair endothelial function [57] and increase plasma viscosity and fibrinogen [58]. Nakamura and colleagues treated arteriosclerosis obliterans patients on chronic hemodialysis with LDL-apheresis (Liposorber), and demonstrated significant decreases in carotid IMT and improved pulse wave velocity of the posterior tibial arteries [30,59]. In another study by Nakamura [60], eight patients with long-standing Type 2 diabetes and nephrotic syndrome were treated 12 times with the Liposorber over a 9-week period, resulting in a significant reduction of creatinine, blood urea nitrogen, urinary protein excretion, number of podocytes and increased creatinine clearance. Nakajima revealed that the use of LDL-apheresis (Liposorber) resulted in a significant reduction of urinary proteins and increased creatinine clearance compared with controls [61]. Muso and colleagues used LDL-apheresis (Liposorber) treatment for patients with steroid-resistant nephrotic syndrome and significantly lowered their urinary protein and increased serum albumin when compared with the steroid-treated control group [62].

**Ocular microcirculatory disturbances**

Nonarteritic acute anterior ischemic optic neuropathy (NAION) is the most common cause of acute optic nerve disease in adults over 50 years of age and can lead to irreversible vision loss [63]. The disease is thought to be the result of insufficient blood supply to the optic nerve, with no generally agreed therapy. Risk factors include atherosclerosis, diabetes and increased blood viscosity [64,65]. In a study using HELP therapy, 11 patients with NAION were treated three times over a 2-week period and showed improvements in their visual field and visual acuity when compared with controls [52,66].

**Sudden idiopathic hearing loss**

Elevated plasma levels of fibrinogen or cholesterol, and the subsequent increase in viscosity, may result in altered blood flow, local hypoperfusion and hearing loss [67]. A multicenter study involving 201 patients with idiopathic sudden-onset sensorineural unilateral hearing loss revealed one treatment of LDL-apheresis (HELP) was as effective as conventional therapy, particularly in patients with elevated plasma fibrinogen and LDL [68].

**Conclusion**

LDL-apheresis is a safe and effective procedure for lowering plasma cholesterol and reducing cardiovascular events in patients with uncontrolled hypercholesterolemia. However, only a small fraction (<250) of potentially eligible candidates (>6000) receive LDL-apheresis therapy in North America. The barriers that may influence the low
number of patients receiving LDL-apheresis include cost of treatments (US$45,000–100,000 per year), training of nursing staff and convincing patients of the need for chronic therapy.

Recent clinical trials demonstrating the benefit of aggressive LDL reduction and the association of vascular inflammation to an increased risk of CVD further support the use of apheresis for qualified patients as designated by the present guidelines.

Future perspective

The development of more potent lipid-lowering medications may reduce the number of patients who now qualify for LDL-apheresis. The current guidelines requiring LDL levels of greater than 200 mg/dl, before initiating apheresis, might be adjusted more towards a patient's cardiovascular instability and lack of alternative care. For example, an individual who has ongoing unstable angina and LDL of 130 mg/dl, despite maximum lipid lowering and anti-angina treatments, may benefit from LDL-apheresis.

Finally, the future of LDL-apheresis may be in the field of acute vascular disease. The multiple and immediate changes to the vascular system by LDL-apheresis may warrant its use for a vast number of acute situations such as those already described in this review. These and other potential applications for LDL-apheresis require validation by further scientific research.

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**Executive summary**

**Introduction**

- The National Cholesterol Education Program (NCEP) expert panel recommends reducing plasma levels of low-density lipoprotein cholesterol (LDL-C) as a primary target of lipid-lowering therapy. There are still a sizable percentage of patients who, for genetic reasons and/or because of resistance to therapy, are unable to reach appropriate plasma levels of cholesterol with standard lipid-lowering therapies.

**LDL-apheresis**

- LDL-apheresis is an approved chronic maintenance therapy for the lowering of plasma cholesterol (LDL reduction >60%) in patients with uncontrolled hypercholesterolemia caused by genetics and/or resistance to pharmacotherapy.
- Common LDL-apheresis methods include immunoabsorption, dextran sulfate cellulose (DSA), heparin extracorporeal LDL precipitation (HELP), direct adsorption of lipoprotein and double filtration.
- Only the DSA and HELP are approved in the USA and their ability to lower plasma cholesterol is related to the binding of apolipoprotein (apo)B-lipoproteins to the dextran sulfate filter (DSA [Liposorber] system) or precipitation of positively charged apoB-lipoproteins when heparin is added at a low pH (HELP).
- Clinical studies have demonstrated the benefit of LDL-apheresis in the reduction of cardiovascular disease.

**In addition to cholesterol, LDL-apheresis lowers other pathologic markers of vascular disease**

- Inflammation; markers approved include C-reactive protein, lipoprotein-associated phospholipase A2, fibrinogen, E-Selectin, vascular cellular adhesion molecule-1, intercellular adhesion molecule-1, monocyte chemoattractant protein-1, lipopolysaccharide binding protein, matrix metalloproteinase-9, and tissue inhibitor of metalloproteinase-1.
- Hemorheology (blood viscosity): LDL-apheresis, after one treatment, reduces blood viscosity by 20% and remains lowered for at least 1 week. The ability to acutely improve blood viscosity can have an immediate effect on vascular flow and may help explain the rapid recovery in myocardial blood flow and minimum coronary resistance seen in patients with coronary artery disease after one treatment of LDL-apheresis.
- Thrombosis and fibrinolysis: LDL-apheresis can efficiently lower coagulation factors involved in the prothrombotic pathway. Factors include; tissue factor, von Willebrand factor, Factor V, Factor VII, soluble CD40 ligand (sCD40L), homocysteine and fibrinogen. LDL-apheresis can also lower markers that promote the fibrinolytic cascade including: plasminogen, protein S, protein C and antithrombin.
- Lipoprotein (Lp)(a), small dense LDL, oxidized LDL and vascular motion; Lp(a) is associated with the induction of adhesion molecules, foam cell formation, plaque inflammation, inhibition of nitric oxide (NO) and increased thrombosis. LDL-apheresis is presently the only treatment that significantly reduces Lp(a) levels. LDL-apheresis may also cause a relative increase in large LDL-subfractions and a concomitant decrease of small dense LDL. LDL-apheresis significantly lowers pro-inflammatory oxidized-LDL, which correlates with the increase of NO levels and vasodilatation. Besides NO, other mediators of vasomotion improved by LDL-apheresis include bradykinin, endothelin-1 and PG12.
**Executive summary**

**Alternative clinical applications of LDL-apheresis**
- The use of apheresis has been studied in various vascular diseases such as:
  - Peripheral vascular disease; where it decreases or reverses the progression and symptoms.
  - Cerebral vascular disease; changes to cerebrovascular function, improves CO2 reactivity, plasma viscosity and reduces rheological markers.
  - Cardiac transplantation; increases mean luminal diameter and reduces graft vessel disease in cardiac transplant patients.
  - Renal disease; decreases urinary proteins, increases creatinine clearance and increases serum albumin in renal patients.
  - Ocular microcirculatory disturbances; patients with acute anterior ischemic optic neuropathy experience improvements in the visual field and visual acuity.
- Sudden idiopathic hearing loss; patients with sudden-onset sensorineural hearing loss in one ear found a single treatment with HELP to be as effective as conventional therapy.

**Summary & conclusions**
- LDL-apheresis is a safe and effective procedure for lowering plasma cholesterol and reducing cardiovascular events in patients with uncontrolled hypercholesterolemia.
- The future of LDL-apheresis could be in the field of acute vascular disease.
- Potential applications for LDL-apheresis require validation by further scientific research.
Vascular benefits of LDL-apheresis for patients with peripheral vascular disease.


**Significant improvement of kidney function for patients with the nephrotic syndrome following a series of LDL-apheresis (Liposorber)**


**LDL-apheresis improves visual acuity for patients with a generally untreatable ocular disease.**


**Multicenter trial demonstrating the benefits of LDL-apheresis (heparin extracorporeal LDL precipitation) for idiopathic hearing loss.**

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