Role of Lipoprotein Apheresis in Cardiovascular Disease Risk Reduction

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Keywords

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Abstract

Background and Aim: Elevated low-density lipoprotein cholesterol and/or lipoprotein(a) are established risk factors for cardiovascular disease (CVD). Management of hypercholesterolemia consists of drug therapies, including statins and proprotein convertase subtilisin/kexin type 9 inhibitors. In patients with familial hypercholesterolemia (FH), lipoprotein apheresis (LA) is utilized to control lipid levels. However, LA is not currently a standard therapy for non-FH. This review summarizes the literature regarding LA therapy in CVD prevention. **Methods:** PubMed/MEDLINE databases were searched using the keywords "LA" and "CVD". Citations were individually reviewed for relevance. **Results:** The efficacy of LA was clearly demonstrated, largely based on evidence from observational studies. In patients who are unresponsive to traditional lipid-lowering medications, LA effectively reduced serum lipoprotein levels and adverse cardiovascular events. **Conclusion:** It was concluded that LA is a safe and effective technique that could be considered in the manage-

ment of hypercholesterolemia and future risk. Randomized control trials would further support a role for LA as a therapeutic option.

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Introduction

Approximately 11.5% (27.6 million) of American adults are suffering from heart disease. The American Heart Association (AHA) has estimated that by 2035, 45.1% of the US population will have some form of heart disease [1]. Important risk factors for cardiovascular disease (CVD) include high blood pressure, smoking, and high cholesterol, and 47% of Americans have at least one of these risk factors [2]. Following the discovery of the low-density lipoprotein (LDL) receptor [3] and advent of statins in the 1980s, reduction of high cholesterol levels has become an important therapeutic target in primary and secondary prevention of CVD. Numerous studies have confirmed elevated LDL as a well-established pro-atherogenic factor contributing to CVD [4, 5].

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LDL consists of a core component containing primarily cholesteryl esters, surrounded by a phospholipid monolayer and a single polypeptide chain of apolipoprotein B-100 (apoB-100) [6, 7]. It is the main transporter of plasma cholesterol, carrying approximately 65–70% [8]. Different LDL subtypes, dependent on size and composition, vary in atherogenic potential [9–11]. Smaller, dense LDL molecules are more associated with atherogenesis, increased triglyceride, and reduced high-density lipoprotein (HDL) levels, as well as metabolic syndrome and diabetic complications [11–14]. Dysregulation of cholesterol transport due to mutation of the LDL receptor or the apoB-100-binding protein, as is the case in familial hypercholesterolemia (FH), can lead to severely elevated levels of LDL and premature coronary artery disease (CAD) [3, 15, 16].

In addition to LDL, evidence has indicated a role for lipoprotein(a) (Lp[a]) as a predictive factor for CVD [17, 18]. Lp(a) contains apoB-100, as well as an additional apo(a) [19]. The apo(a) chain differentiates Lp(a) from LDL and is similar in structure to plasminogen, a protein involved in fibrinolysis [20]. Lp(a) levels are heterogeneous in nature and determined genetically via the *LPA* gene locus [21]. Specific single-nucleotide polymorphisms have been identified within this gene that influence baseline Lp(a) concentrations, with correlations to CAD [22]. The LDL receptor is not the primary receptor responsible for Lp(a) uptake from plasma [23]. Accordingly, Lp(a) levels do not respond well to statin therapy [24–26]. This paper will review the pathophysiology of LDL and Lp(a) in CVD, role and the current evidence surrounding lipoprotein apheresis (LA) in CVD risk reduction in patients with elevated LDL and/or Lp(a) levels.

The PubMed/MEDLINE database was searched using the terms “LDL apheresis” and “CVD” to look for studies regarding the use of LDL apheresis in CVDs. Citations were individually reviewed for relevance. Articles involving the use of LDL apheresis in non-CVD conditions were excluded. There is a lack of randomized control trials (RCTs) studying the efficacy of LA compared to standard lipid-lowering medical therapy. The majority of studies published are observational, either retrospective and/or prospective.

Role of LDL and Lp(a) in CVD

Pathophysiology of LDL

Many studies have confirmed an atherogenic role for LDL cholesterol. It is theorized that retention of lipopro-

teins within the vasculature wall is the initiating event in atherosclerosis [27]. LDL can bind to vessel walls via an apoB-binding site, which interacts with extracellular matrix proteoglycans including decorin, biglycan, and syndecan-4 [28]. This lipid accumulation increases when circulating LDL levels are chronically elevated [29, 30]. Retained LDL is modified to become oxidized-LDL (oxLDL), a necessary step for progression of atherosclerosis. OxLDL activates endothelial cells by inducing expression of cellular adhesion molecules, including P-selectin, allowing for migration of leukocytes into the endothelium [31]. Macrophage endocytosis of oxLDL leads to foam cell formation and subsequent appearance of fatty streaks within the vessel wall [32–34]. This process releases a number of cytokines involved in atherogenesis, including IFN- γ , TNF- α , and IL-1 [35, 36]. oxLDL can promote vascular smooth muscle cell proliferation, which migrate into the area forming a fibrous cap over the accumulation of lipids and foam cells [37, 38]. Continued chronic inflammation causes macrophage and smooth muscle cell apoptosis, as well as proteolytic enzyme release leading to collagen degradation [39]. These processes create a vulnerable plaque at risk of rupture, creating the potential for adverse cardiac events.

Cardiovascular Risk Associated with Elevated LDL

Evidence of a link between elevated cholesterol and CVD has been well-established [4, 5]. Stamler et al. [4] screened 347,978 men from 1973 to 1975 with an average 12-year follow-up period for risk factors including diabetes mellitus, serum cholesterol levels, and smoking. It was concluded that serum cholesterol was a significant risk factor in cardiovascular mortality, in the presence/absence of diabetic comorbidity [4]. In 2016, the Prospective Studies Collaboration performed a meta-analysis of 61 prospective studies of vascular mortality, including 55,000 vascular deaths, and determined that total cholesterol levels were positively associated with vascular mortality due to ischemic heart disease [40]. Further studies have indicated a direct link between oxLDL and coronary heart disease risk, in elderly populations and those with metabolic syndrome [41–43].

The introduction of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statin) therapy allowed for definitive studies that correlate elevated LDL cholesterol levels with CVD risk. The Cholesterol Treatment Trialists' Collaboration published a landmark meta-analysis of statin therapies, in which they analyzed data from 90,056 participants in 14 randomized statin-based trials [44]. They demonstrated a 12% reduction in all-cause

mortality per mmol/L reduction in LDL cholesterol, noting a reduction of one-fifth mmol/L LDL reduction could significantly reduce the 5-year incidence of cardiovascular events. A second meta-analysis published 5 years later compared more vs. less intensive statin therapy regimens [45]. It was demonstrated that a 1 mmol/L reduction in LDL cholesterol could reduce the annual rate of myocardial infarction and coronary artery revascularization by approximately 20%.

Lastly, the link between elevated LDL and CVD is exemplified by inherited diseases causing aberrant LDL metabolism. FH is typically an inherited autosomal dominant disorder leading to defective clearance of LDL from the blood and is characterized by high circulating levels of LDL cholesterol [46]. Patients with homozygous or heterozygous FH are at increased risk for premature coronary heart disease and require screening and intensive LDL cholesterol-lowering therapy [47].

Pathophysiology of Lp(a)

Similar to LDL, oxidized Lp(a) (OxLp[a]) has a stronger role in atherogenesis than naïve (nonoxidized Lp[a]) [48]. OxLp(a) is shown to localize in endothelial cells early in the atherogenic process, implying that it may also be a part of the initial dysfunction in atherogenesis [49]. There are several additional parallels between Lp(a) activity and LDL activity in plaque formation, including macrophage endocytosis to form foam cells, endothelial cell activation, and stimulation of vascular smooth muscle cell proliferation [50–53].

Unique to Lp(a), studies suggest a role in the fibrinolytic system, based on the homology of the apo(a) protein with plasminogen. The normal conversion of plasminogen to plasmin is an important step in fibrinolysis. Lp(a) can inhibit plasmin formation in vitro, suggesting a potential antifibrinolytic role [54, 55]. Further, Lp(a) can also increase the activity of plasminogen activator inhibitor in vitro [56]. Taken together, these studies highlight the contributions of Lp(a) to atherogenesis in a similar manner to LDL, as well as its unique proposed antifibrinolytic properties.

Cardiovascular Risk Associated with Elevated Lp(a)

The link between Lp(a) and CVD risk is not as established as LDL cholesterol; however, there is strong evidence that Lp(a) levels are a significant baseline risk factor. Assessment of Scandinavian Simvastatin Study patients revealed that subjects with major cardiovascular events had higher levels of Lp(a), which was also a predictor of mortality [17]. Other studies have demonstrated

that Lp(a) is a significant risk factor in patients with previously existing CVD [57–59]. In 2014, a study by Khera et al. [60] found that Lp(a) levels were a determinant of residual risk in patients who had undergone statin therapy. Of note, Lp(a) levels are also an independent risk factor in FH, and levels are shown to be higher in those with FH [61].

There appears to be a cumulative effect in which the combination of elevated LDL and Lp(a) levels increases the overall risk. The Prospective Cardiovascular Münster study followed 788 male participants for 10 years, measuring baseline risk factors including Lp(a) levels, LDL and HDL cholesterol, and triglycerides [62]. Lp(a) was shown to be an independent risk factor, increasing the risk of a coronary event by 2.7 times if serum Lp(a) was >0.2 g/L.

Lp(a) levels remain a significant risk factor in patients who have received therapeutic intervention for their coronary heart disease [63]. One study assessed long-term (15 year) cardiovascular outcomes in patients who had undergone coronary artery bypass grafting, and indicated Lp(a) levels were an independent risk factor, causing a 3-fold increase in risk of major cardiovascular events [64]. Lastly, Lp(a) levels are implicated in non-coronary types of CVD, including stroke [65], peripheral arteriosclerosis [66] and aortic valve stenosis [67, 68].

Current Standard of Care for Elevated LDL and Lp(a) Levels

According to the 2013 AHA/American College of Cardiology guidelines, the current approach to elevated blood LDL-cholesterol begins with lifestyle modifications, including proper diet, regular exercise, and smoking cessation [69]. Statin therapy remains the first-line drug treatment for elevated LDL level and is indicated in both primary and secondary prevention of CVD [70]. There are currently no therapeutic targets for LDL levels recommended by the American College of Cardiology/AHA; rather, statin dosing is guided by the patient's individual risk level. High-intensity statin therapy can result in LDL reduction of >50%, while moderate-intensity statin therapy typically results in 30–50% reduction. Statins are relatively safe; side effects are uncommon and generally muscle related [71].

If patients are intolerant or unresponsive to statin therapy, adjunct therapies may be added. Generally, ezetimibe, which acts to decrease cholesterol absorption in

the small-intestine, is the first choice for adjunct therapy and has additional benefit combined with statin therapy [72, 73]. Alternative adjunct therapies include bile acid-binding resins (colesevelam, colestipol) and niacin [74, 75]. A recent development is proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors (alirocumab and evolocumab), human monoclonal antibodies that increase LDL receptor density by inhibiting binding of PCSK9 to the LDL receptor [76, 77]. Patients with homozygous FH do not respond as well to statins due to severely elevated LDL levels and require high-intensity dosing regimens [78] and adjunct therapy [76, 79]. Additional adjunct therapies used primarily for FH, mipomersen, and lomitapide have significant hepatotoxicity [80]. For these patients, LA is a beneficial and often necessary intervention.

Unlike LDL, statins are largely ineffective in reducing Lp(a) levels [25]. To treat Lp(a) hyperlipoproteinemia, high-dose niacin can reduce Lp(a) levels by 20–40% [81, 82]. PCSK9 inhibitors can also improve Lp(a) levels, although not as effectively as their action on LDL. Data from recent clinical trials with alicumab [77] and evolocumab [83] demonstrated reduction of Lp(a) by 20–30%.

Lipoprotein Apheresis in Cardiovascular Disease

LA was first introduced as a treatment option for homozygous FH in the mid 1970s. A paper in France published in 1967 outlined the use of experimental plasmapheresis to reduce manifestations of FH [84]. Following this, Dr. Thompson et al. [85] in London, England, treated his patients suffering from FH with the experimental technique (Thompson et al. [85]). Dr. Lupien et al. [86], a Canadian physician, developed a manual heparin-based protocol that effectively reduced LDL levels in his patients. From the 1970s until present day, several different LA techniques have been developed.

LA is capable of removing both LDL and Lp(a) from the blood [87]. In FH, a single treatment of LA can reduce LDL by 65–70%. LA for elevated LDL levels has FDA approval in the following situations: patients with homozygous FH with >500 mg/dL LDL, heterozygous FH with no known CVD and >300 mg/dL LDL, or with known CVD and LDL >200 mg/dL [70]. It is recommended that LA begin in early childhood (ages 6–7) for homozygous FH patients to reduce the risk of CVD, particularly aortic valve stenosis [82]. In North America, LA is not the standard treatment option in patients with non-FH related

hypercholesterolemia. However, guidelines vary by country. Germany has LA indications for LDL 120–130 mg/dL and progressive CVD, or isolated Lp(a)-hyperlipoproteinemia (>60 mg/dL) and progressive CVD. Japan has approved LA use in patients with CAD and total cholesterol >250 mg/dL [88].

Further, LA is effective in reducing Lp(a) in situations of Lp(a)-hyperlipoproteinemia with subsequent reduction of CVD risk and can be beneficial in patients who are receiving maximal medication doses [89]. LA can reduce Lp(a) by 40–88% [82]. The American Society for Apheresis recommends the use of LA in Lp(a)-hyperlipoproteinemia. However, treatment is limited in the United States due to the scarcity of the centers offering LA, as well as the high cost [88].

The benefit of LA has also been suggested in several other medical conditions. Notably, LA in nephrotic syndrome can improve proteinuria and lipid levels, preventing the progression of renal disease [90–92]. LA has also been utilized in sudden sensorineural hearing loss [93], diabetic foot ulcers [94], and peripheral artery disease [95]. In addition to reduction of lipid levels, LA therapy also reduces inflammatory markers (including C-reactive protein and cellular adhesion molecules) [96–101] and circulating coagulation proteins (including fibrinogen and tissue factor) [102, 103]. A protective role for LA therapy in reducing oxidative burden has been demonstrated [104, 105].

LA Techniques

Early lipid apheresis techniques utilized plasmapheresis principles to filter lipids out of plasma [84, 85]. This nonspecific method required a filter with a defined pore size that effectively removed larger particles including LDL from plasma. A semi-selective process was later introduced that involved the use of a second filtration membrane (known as membrane differential filtration, double filtration) [106], but was still less specific than other targeted LA techniques.

Immunoadsorption

Heparin anticoagulation is indicated for this method. Blood is collected via vascular access and plasma is isolated. Plasma is filtered through 1 of 2 twin columns containing purified sheep antibodies that bind to ApoB-100. The antibodies are covalently linked to sepharose particles on the columns. Plasma flow alternates between columns; while one column is acting as the adsorption col-

umn, the other column is regenerating. Regeneration occurs using a glycine buffer solution followed by a saline wash. Columns are regenerated and stored in sterile conditions, then can be reused for later apheresis sessions [107]. This treatment can reduce LDL and Lp(a) levels by approximately 55% [90].

Dextran Sulfate Cellulose Absorption

The Liposorber LA-15 system was approved by the FDA in 1996 for indications of LDL hypercholesterolemia [108]. Heparin use is indicated to prevent extracorporeal clotting. Vascular access is achieved and blood is segregated, isolating the plasma component. Plasma flows through 1 of 2 dextran sulfate cellulose (Liposorber) 150 mL columns, during which time binding of dextran sulfate to ApoB-100 protein captures ApoB-100 bound proteins including LDL, VLDL, and Lp(a). Flow is alternated between columns, allowing for each to regenerate before returning plasma flow to the area. Plasma and red blood cells are pooled and the patient is reinfused [109]. LDL levels can be decreased up to 76–81%, and Lp(a) levels from 65 to 70% [110].

The Liposorber D uses a whole-blood technique in which plasma is not isolated prior to flow through the adsorption column [111]. The column contains negatively-charged dextran sulfate cellulose beads that can bind to ApoB-100 molecules (including LDL, VLDL, and Lp[a]). This method reduced LDL and Lp(a) by 62.2 and 55.6%, respectively, with a single LA treatment [111].

Heparin Extracorporeal LDL Precipitation

This method is similar to the Liposorber technique, but heparin is used as a binding agent to ApoB-100 [112]. Plasma is isolated, treated with a heparin buffer solution at a pH of 4.85, causing lipoprotein precipitation with fibrinogen and heparin. The LDL precipitate is filtered from the plasma, and excess heparin is adsorbed via filtration columns. Bicarbonate buffer dialysis is done to neutralize the pH of the plasma, before pooling with the red blood cell component and reinfusion of the patient [113, 114]. This method can reduce LDL and Lp(a) by 60% in a single session [115, 116]. Further, it can also increase HDL over baseline levels in the long term (12-month follow-up) [116].

Direct Adsorption of Lipoprotein Using Hemoperfusion

Heparin anticoagulation is indicated for this treatment [117]. The Direct Adsorption of Lipoprotein method uti-

lizes a negatively charged matrix of polyacrylate bound to polyacrylamide beads. Whole blood is perfused through the absorption matrix, which can effectively bind LDL, VLDL, triglycerides, and Lp(a), while HDL is not affected. The pores of the beads are sufficiently small to avoid immobilization of red blood cells. The lipoproteins are eliminated, and the whole blood is reperfused back into the patient. This treatment is relatively simple and effective, reducing LDL and Lp(a) by over 60% per session [107, 118].

Specific Lp(a) Apheresis

There is currently only one Russian device on the market that can specifically remove Lp(a) from the blood [119]. In a similar manner to immunoadsorption, this method uses 2 sepharose columns bound to anti-Lp(a) monospecific polyclonal sheep antibodies. These columns can be regenerated for the patient in future treatments. This treatment has been shown to reduce Lp(a) levels by up 88%, with unchanged LDL levels [119, 120].

Effect of LDL Apheresis on CVD Outcomes

Select studies assessing the effect of LA on cardiovascular outcomes are summarized in Table 1. Studies of LA effect on other outcomes (atherosclerosis, carotid artery stenosis, peripheral artery disease) are discussed below but not included in Table 1. A prospective, observational multicenter study published by the Pro(a)LiFe study group in Germany assessed the impact of chronic LA in 170 patients receiving therapy for Lp(a)-hyperlipoproteinemia and progressive CVD [121]. The initial study was published 2 years post commencement of LA therapy. Incidence rates of cardiovascular events, 2 years prior to commencing LA and 2 years post were compared. Average annual rates for adverse cardiovascular events (ACVE) decreased from 0.41 in the 2 years prior to LA, to 0.09 2 years after starting LA therapy. The first year of LA therapy resulted in 0.14 decline in ACVE, followed by 0.05 decline in the second year of therapy. In 2017, a follow-up study was published with the same cohort of patients, 5 years after starting LA therapy [122]. A total of 154 (90.6%) patients completed follow-up to 5 years, where incidence of ACVE declined to a mean of 0.06.

Several other retrospective studies indicated a link between LA and improved cardiovascular outcomes, in patients with elevated Lp(a) levels. A retrospective analysis of 37 patients receiving weekly LA treatments resulted in a reduction of Lp(a) levels by 68%. Cardiovascular event-free

Table 1. Summary of studies on LA for CVD prevention in patients with hypercholesterolemia

Study	n value	Age of patients, mean $\pm$ SD	LDL technique	Primary disease	Pretreatment labs and other characteristics	Treatment	Outcome
Bigazzi et al. [151], 2018 – Multicenter retrospective study	23	Mean age 63 $\pm$ 9 years	HELP (16/23), dextran sulfate (4/23), cascade filtration (2/23), immunoadsorption ion (1/23)	Hyper Lp(a), progressive CVD on lipid-lowering therapy	Pre-LA LDL-cholesterol <100 mg/dL. Recorded ACVE prior to LA = 40, event rate of 0.43/year	Average frequency of 14 days between LA treatments Duration of LA: median of 7 years (interquartile range of 3–9 years)	Recorded ACVE = 10, event rate of 0.11/year (74% reduction in event recurrence)
Graesdal et al. [152], 2012 – Observational study	7	Mean age at first LA 10 (6–44) years	Whole-blood column (5/7), plasma filtration (2/7)	Homozygous FH	Median LDL at diagnosis – 704 (592–1,268) mg/dL	LA performed 1 time/week Average duration of LA at time of follow-up = 12.57 years	Median LDL post-apheresis – 85 (50–108) mg/dL. Cardiovascular manifestations progressed in most patients despite therapy
Heigl et al. [126], 2015 – Retrospective, monocentric study	118	Mean age 59.6 years	HELP apheresis, DFPP, DALI	Severe hypercholesterolemia or Lp(a)-hyperlipoproteinemia	Patients with severe hypercholesterolemia: Mean LDL = 176.4 $\pm$ 67.0 mg/dL Mean Lp(a) = 75.0 $\pm$ 64.5 mg/dL MACE = 167 ACVE = 184 Patients with isolated Lp(a)-hyperlipoproteinemia Mean LDL = 96.1 $\pm$ 33.5 mg/dL Mean Lp(a) = 127.2 $\pm$ 67.3 mg/dL MACE = 94 ACVE = 105	Frequency unknown Mean individual period of LA therapy = 6.8 $\pm$ 4.9 years Reduction in MACE – 73.7% Reduction in ACVE – 64.1% Patients with isolated Lp(a)-hyperlipoproteinemia: Mean total LDL reduction – 22.7 $\pm$ 31.2% Mean total Lp(a) reduction – 52.8 $\pm$ 23.0% Reduction in MACE – 90.4% Reduction in ACVE – 89.5%	Patients with severe hypercholesterolemia: Mean total LDL reduction – 32.1 $\pm$ 19.6% Mean total Lp(a) reduction – 56.4 $\pm$ 20.5% Reduction in MACE – 73.7% Reduction in ACVE – 64.1% Patients with isolated Lp(a)-hyperlipoproteinemia: Mean total LDL reduction – 22.7 $\pm$ 31.2% Mean total Lp(a) reduction – 52.8 $\pm$ 23.0% Reduction in MACE – 90.4% Reduction in ACVE – 89.5%
Jaeger et al. [89], 2009 – Longitudinal, multicenter cohort study	120	Mean age 54.4 $\pm$ 10.6 years	HELP, DALI, dextran sulfate, DFPP, and immunoadsorption ion	CAD and refractory to lipid-lowering therapy	Lp(a) levels $\geq$ 2.14 μ mol/L, median Lp(a) – 4.00 μ mol/L Annual MACE rate – 1.056	LA therapy every week, 2 weeks, or 10 days for a minimum of 3 months Mean duration for LA therapy: 5.0 $\pm$ 3.6 years	Median Lp(a) – 1.07 μ mol/L Annual MACE rate – 0.144
Khan et al. [125], 2017 – Single blinded randomized cross-over study	20	Mean age 60.9 years	Dextran sulfate	Refractory angina and raised lipoprotein(a) >500 mg/dL	Mean LDL – 2.16 mmol/L Mean Lp(a) – 1,100 mg/L Median total carotid volume (mm ³): 2,482	LA performed 1 time/week for 3 months	Myocardial perfusion reserve (MPR): Increased by +0.47 compared to sham group –0.16 (net treatment increase of 0.63 between groups) Median total carotid volume (mm ³): 2,251 Improvement in 4/5 domains of Seattle Angina Questionnaire (SAQ) during apheresis Reduction in Lp(a) following apheresis: –679.5 mg/L Reduction in LDL following apheresis: – 1.55 mmol/L

Table 1. (continued)

Study	n value	Age of patients, mean ± SD	LDL technique	Primary disease	Pretreatment labs and other characteristics	Treatment	Outcome
Mellwig et al. [153], 2017 – Retrospective single center observational study	2,023	Mean age 60.04±0.58 years	DALI and HELP	High Lp(a) levels and documented coronary heart disease	Mean LDL – 144.39 ± 92.01 mg/dL Mean Lp(a) – 133.04 ± 39.68 mg/dL 49 PCI and 2 CABG prior to LA initiation	LA performed 1 time/week for follow-up period of 69.38±71.67 months	Mean LDL – 99.43±36.53 mg/dL Mean Lp(a) – 91.13±33.02 mg/dL In 59.87±49.49 months, 15 patients did not require additional PCI In 69.38±71.67 months, 8 patients required further PCI (14 PCI total) Reduction of PCI by 71.43%
Pro(a)liFe – Leebman et al., [121] 2013 – Prospective, observational multicenter study	170 in 2 year follow-up, 154 at 5 years	Mean age 57 years at first LA treatment	Temperature optimized DFPP, HELP, DALI, dextran sulfate from plasma and whole blood, ApoB100 immunoadsorption	Lp(a)- hyperlipoprotei nemia and progressive CVD	Prior to LA: mean LDL = 99.0±40.1 mg/dL, mean Lp(a) = 104.9±45.7 mg/dL Major adverse CV events was 0.41, years (first study) up to 2 years prior to LA	LA performed twice per week in 3 patients, weekly in 157, biweekly in 9 and every 3 weeks in 1, for period of 2 years (first study) up to 5 years (second study)	Mean annual incidence rate of cardiovascular events was decreased to 0.09 in the 2 years following commencement of LA, 0.06 in 5 years following LA
Pro(a)liFe – Klingel et al. [122], 2017 (5-year follow-up of above study)							
Rosada et al. [123], 2014 – Retrospective analysis	37	Mean age 58 years ±11 years	HELP, dextran sulfate, DALI	Isolated Lp(a)- hyperlipoprotei nemia and coronary heart disease	Mean LDL = 84 mg/dL ± 21 Mean Lp(a) = 112 mg/dL ± 34 Cardiovascular event-free survival rate pre-apheresis = 38%	LA performed 1 time/week for 6.8±3.9 years (range 1.6–16.5 years)	Mean Lp(a) = 36.2±11.6 (–68%) mg/dL Cardiovascular event-free survival rate = 75% 1 year after apheresis began, 61% 5 years after apheresis began
Sachais et al. [154], 2005 – Retrospective analysis	34	Mean age 50 years, ranged from 18 to 67 years	Dextran sulfate	Patients had to meet one of the following criteria: LDL 500 mg/dL (functional FH homozygotes) No CHD and LDL 300 mg/dL on maximally tolerated drug therapy CHD and LDL 200 mg/dL with maximally tolerated drug therapy	Values not provided	LA therapy performed every 2 weeks, for an average of 2.5 years (range: 3 months to 7 years)	Posttreatment with LA (average 2.5 years): 3.2 fold decrease in CVE Over 20 fold decrease in cardiovascular interventions
Sampietro et al. [130], 2015 – observational, single-center study	30	Mean age 62±8 years	Dextran sulfate (18/30), HELP (12/30)	FH or FCH, with or without hyper-Lp(a), with CVD and on maximal lipid-lowering therapy (11 CABG, 10 PTCA/stenting, 6 both)	At first LA, 90% of patients had undergone previous coronary revascularization (11 CABG, 10 PTCA/stenting, 6 both) 86 ACVE observed before therapy (ACVE rate/year of 0.58)	LA therapy performed biweekly for a median of 5 years (interquartile range 3–8 years)	15 ACVE observed during therapy (ACVE rate/year of 0.13)

Table 1. (continued)

Study	n value	Age of patients, mean ± SD	LDL technique	Primary disease	Pretreatment labs and other characteristics	Treatment	Outcome
Schatz et al. [124], 2017 – Multicenter observational study	113	Mean age 56.3 years	Not stated	3 patients groups: Elevated LDL – Lp(a) <600 mg/L, LDL-C >2.6 mmol/L Elevated Lp(a) – (Lp(a) >600 mg/L, LDL-C <2.6 mmol/L) Both elevated Lp(a) and LDL – Lp(a) >600 mg/L, LDL-C >2.6 mmol/L	CV events per patient prior to LA: Group 1 – 0.59±0.63 Group 2 – 1.57±1.31 Group 3 – 1.27±1.1	LA therapy was performed 1 time/week for 2 years prior to data collection	CVE per patient after LA start: Group 1 – 0.28±0.53 (53% reduction) Group 2 – 0.36±0.83 (77% reduction) Group 3 – 0.32±0.82 (74% reduction)
Schettler et al. [127], 2017 – Observational study including retrospective and prospective data	1,283	Majority >60 years (ranged from 20 to 90 years)	Not stated	High LDL cholesterol and/or high Lp(a) levels with progressive CVD	45% had Lp(a) levels >60 g/dL, 35% had LDL levels >100 mg/dL, and 20% of patients had mixed dyslipidemia of both groups	LA therapy was performed for one year prior to data collection, frequency not stated (15,167 treatments total for 1,283 patients)	Median LDL reduction of 68.6% Median Lp(a) reduction of 70.4% MACE reduction of 97% in the first year of LA treatment
Thompson et al. [129], 1995 – FH Regression Study – randomized control trial	39 (20 patients undergoing LA, 19 control patients)	Mean age of apheresis group (SD) – 49.2 (7.8) years Mean age of medication only group (SD) – 49.8 (7.4) years	Dextran sulfate	Heterozygous FH and coronary artery disease	Apheresis group: Mean baseline LDL (SD) – 6.8 (2.2) mmol/L Mean baseline Lp(a) – 47 (25) mg/dL Medication only group: Mean baseline LDL (SD) – 6.1 (1.8) mmol/L Mean baseline Lp(a) – 34 (12) mg/dL	LA therapy performed once/2 weeks, for a mean of 2.1 years	Apheresis group: Mean LDL (SD) – 3.2 (0.8) mmol/L Mean Lp(a)(SD) – 33 (14) mg/d Medication only group: Mean LDL (SD) – 3.4 (1.1) mmol/L Mean Lp(a) (SD) – 45 (21) mg/dL No significant difference in primary angiographic endpoints (mean % diameter of stenosis)
Van Buuren et al. [131], 2012 – Retrospective study	27	Mean age = 49.2, ranged from 10–67	HELP apheresis	Familial hypercholesterolemia, 26/27 had coronary artery disease	LDL = 223±96 mg/dL Lp(a) 172.9±199.8% 44% had 3 vessel disease	HELP apheresis once weekly (ranged between 50 and 790 treatments)	Mean elimination of was LDL 63.49±7.1% No patients had an MI during LA treatment, 3.7% had one PCI, 11.1% had 2 PCI, 14.8% had 3 PCI and 11.1% >4 PCI
Von Dryander et al. [155], 2013 – observational study	87	Group 1: 55 years Group 2: 61 years Group 3: 53 years	HELP, DALL, lipid filtration, dextran sulfate, immunoadsorption, MONET	Patients defined by 3 groups: Group 1 – LDL >3.4 mmol/L and Lp(a) <600 mg/L; n = 35 Group 2 – LDL <3.4 mmol/L and Lp(a) >600 mg/L; n = 37	Rate of CVE prior to therapy: – Group 1: 2.1 – Group 2: 3.4 – Group 3: 1.8	Median number of years patients underwent LA therapy (frequency not stated): – Group 1: 8.9 years – Group 2: 2.1 years – Group 3: 4.5 years	Rate of CVE during LA therapy (% reduction from 2 years prior to 2 years post-LA therapy): – Group 1: 0.9 (54%) – Group 2: 0.5 (83%) – Group 3: 0.5 (83.5%)

Table 1. (continued)

Study	n value	Age of patients, mean ± SD	LDL technique	Primary disease	Pretreatment labs and other characteristics	Treatment	Outcome
Group 3 – LDL >3.4 mmol/L and Lp(a) >600 mg/L; n = 15							
Yamaguchi et al. [128], 1994 – LDL angioplasty restenosis trial (L-ART), multicenter prospective study	191	Mean age of LA group 57.2±7.7 years Mean age of control group 60.1±8.4 years	Dextran sulfate	Patients receiving PTCA	Median Lp(a) (range) – 28.7 (0.6–207.4) mg/dL Median LDL – 130.8±35.2 mg/dL	First LA treatment performed 2 days prior to PTCA, second treatment performed 5 days post PTCA, continued until data collection 5 months post PTCA	Median Lp(a) (range) – 11.6 (0.5–53.2) mg/dL (57.1±17.7% reduction) Median LDL – 57.3±18.0 mg/dL (55.2±11.0% reduction) Restenosis rate with LA: 18% Restenosis rate w/o LA: 52%

ACVE, adverse cardiovascular events; CAD/CHD, coronary artery/heart disease; CVD, cardiovascular disease; CVE, cardiovascular events; DALI, direct adsorption of lipoprotein; DPPP, double filtration plasmapheresis; FH, familial hypercholesterolemia; HELP, heparin extracorporeal LDL precipitation; LA, lipoprotein apheresis; LDL, low-density lipoprotein; Lp(a), lipoprotein(a); MACE, major adverse cardiovascular events; PTCA, percutaneous transluminal coronary angioplasty.

survival rate increased from 38 to 75%, 1 year after LA therapy began [123]. In 2009, Jaeger et al. [89] demonstrated similar results; LA apheresis lowered mean Lp(a) levels in 120 patients and reduced the rate of major ACVE from 1.056/year to 0.144/year. Last, in 2017, Schatz et al. [124] performed a multicenter observational study, in which they stratified 113 patients into groups dependent on LDL and Lp(a) levels; Group A had elevated LDL, Group B had elevated Lp(a), and Group C had both. They demonstrated that Group B (elevated Lp(a)) had the highest rate of ACVE prior to LA therapy and also had the greatest benefit from LA therapy (77% reduction in ACVE). In a rare cross-over study, Khan et al. [125] assigned 20 patients with refractory angina and elevated Lp(a) to 3 months of LA therapy or 3 months sham, then groups received the alternate treatment for another 3-month period. Results showed a reduction in LDL and Lp(a) levels, as well as increased myocardial perfusion reserve (+0.47) in the LA group compared to the sham group (decreased –0.16).

Additional studies on LA efficacy were observed in patients with LDL elevation, with or without Lp(a) elevation. In 2015, Heigl et al. [126] completed a retrospective analysis of 118 patients with severe hypercholesterolemia or isolated Lp(a)-hyperlipoproteinemia over the course of several years (36,745 treatments). They demonstrated a reduction in LDL and Lp(a) levels in both groups, as well as a reduction in major ACVE of 73.7 and 64.1% for severe hypercholesterolemia and isolated Lp(a)-hyperlipoproteinemia groups, respectively. Further, an observational study based on the German LA Registry assessed 1,283 patients with hypercholesterolemia and/or Lp(a)-hyperlipoproteinemia over the period of 15,167 treatments, across multiple centers [127]. They concluded LA caused a reduction in LDL of 68.6% and Lp(a) 70.4%. Importantly, major ACVEs were reduced by 97% in the first year following initiation of LA therapy. In 1994, Yamaguchi et al. [128] observed the effectiveness of LA in patients receiving PCI (previously termed PTCA), comparing a group of patients who received LA once prior to, and multiple times after their PCI, to a group of patients who did not receive LA. They demonstrated that the restenosis rate following LA (18%) was significantly lower than the restenosis rate without LA (52%).

A subset of studies focused primarily on patients with FH. Thompson et al. [129], published the FH Regression Study, in which they assessed 20 patients with FH undergoing dextran sulfate LA, compared to 19 FH patients who were relying on medication. Although the apheresis group showed marked reduction in both LDL and Lp(a) levels, the progression of atherosclerosis (followed angio-

graphically) was not significantly different between groups. However, other studies have indicated a link between LA and improved CVD in FH patients. Sampietro et al. [130] in 2015 assessed 30 patients with FH or FCH and observed an ACVE rate of 0.58/year prior to LA therapy, with an ACVE rate of 0.13/year following LA. A retrospective analysis of 27 patients with FH who received 8,533 Heparin Extracorporeal LDL Precipitation (HELP) apheresis treatments, with an average follow-up period of 7.0 ± 5.2 years, indicated that LA was successful in reducing LDL levels (average reduction of $63.49 \pm 7.1\%$) and produced low levels of coronary intervention [131].

Effect of LDL Apheresis on Atherosclerosis

The HELP-Study Group published one of the first systematic evidence that HELP apheresis was beneficial in CVD [116]. Thirty nine patients received regular HELP apheresis for 2 years and demonstrated a decrease in the mean degree of stenosis measured angiographically from 32.5 to 30.6%. The LDL-Apheresis Regression study group in Japan assessed changes in coronary artery stenosis angiographically in 37 patients with familial hypercholesterolemia (FH; $n = 32$) or nongenetic hypercholesterolemia ($n = 5$) [132]. They demonstrated that regression of stenosis occurred in 14 patients following >1 year of LA therapy. A similar group in the Netherlands did a 2 year study of 42 men with hypercholesterolemia and progressive CAD [133]. Twenty one men received bi-weekly LA therapy and simvastatin, while a control group received simvastatin alone. LDL reduction was observed in both groups, to a greater extent in the LA therapy group. In 2013, Safarova et al. [134] examined the effects of Lp(a) apheresis therapy on coronary artery atherosclerosis regression, compared to statin therapy alone. Mean diameter stenosis was reduced by -2.0 with LA, while it increased by 3.5 in the statin only group. In 2009, Stefanutti et al. [135] assessed the impact of LA specifically in children with FH ($n = 11$) and concluded that LA resulted in the regression of coronary artery stenosis, and coronary intervention was not required in any patient (patients were evaluated from 2 to 17 years).

Effect of LA on Carotid Artery Stenosis and Peripheral Artery Disease

In 1999, Koga et al. [136] published a study examining the long-term effect of LA on carotid artery atherosclerosis. Eleven FH patients received LA for an average of

7.8 years, while 10 control FH patients received medication only for an average of 5.5 years. LDL levels were reduced significantly with LA, although new plaque formation in the carotid arteries was observed in both groups. However, annual progression rate was slower in the LA group (-0.0023 ± 0.0246 mm/year) compared to the control group (0.0251 ± 0.0265 mm/year). Kroon et al. [137] compared the effects of LA therapy versus statins on the progression of peripheral artery disease, in 42 men with hypercholesterolemia. They demonstrated a reduction in stenosis of the aortotibial tract, as well as a decrease in carotid intima-media thickness in the LA group, while the statin group increased in both aspects. A 2015 study evaluated shear stress on the carotid artery walls during LA therapy in 52 procedures [138]. They demonstrated an initial increase in shear stress, potentially due to the procedure itself, followed by an improvement in shear stress. Lastly, Ezhov et al. [139] demonstrated the benefit of Lp(a)-specific apheresis therapy in 30 patients with CHD. At 9 and 18 months following initiation of LA, changes in carotid intima-media thickness were -0.03 ± 0.09 and -0.07 ± 0.15 mm, respectively, with no significant changes in the control group.

Multiple studies have examined the effects of LA therapy on hemodialysis patients with peripheral artery occlusive disease. Eleven patients underwent 10 sessions of LA and demonstrated corresponding reduction in LDL levels, as well as an increase in endothelium-dependent vasodilation (from 1.6 ± 0.6 to $4.7 \pm 1.0\%$) [140]. In 2 independent case studies in which patients developed intractable ulcers in their feet due to peripheral artery occlusion, LA therapy promoted healing of the wound [141, 142].

Adverse Effects and Precautions for LDL Apheresis

The LA procedure is generally very well-tolerated in the acute and long term, with minimal side effects. A common transient symptom in patients is feeling tension in the legs, potentially in the hands and eyelids as well [143]. Side effects occur in approximately 5.5% of patients and do not appear to differ between LA methods [144]. Vaso-vagal reactions are the most common, presenting as malaise, weakness, or transient hypotension [143]. There is a small risk of hypotension, which can occur in approximately $<1\%$ of patients [144]. Notably, some LA machines can result in significant removal of B12, transferrin, and ferritin causing anemia and may require iron supplementation [145]. One study evaluated 29 patients receiving regular LA to determine impact on their quality

of life (QOL) [146]. Results indicated that patients felt their physical QOL was similar to those of the general population; however, their mental and emotional QOL rated below the general population. It is unknown if the repetitive LA procedure itself can cause emotional or mental distress for patients, or if other factors are causative. There are relatively few contraindications to LA therapy. However, the use of angiotensin-converting enzyme inhibitors are contraindicated [147]. The adsorption process can promote bradykinin release due to the negative charge of the adsorption surface, creating a potential risk for bradykinin syndrome, including hypotension, dyspnea, and shock [148]. Angiotensin II receptor blockers may be used as a substitute medication for blood pressure control, or angiotensin-converting enzyme inhibitor medication may be held for 24 h prior to treatment.

Limitations and Future Directions

The studies discussed above demonstrate a clear benefit for LA therapy in the management of LDL hypercholesterolemia and/or isolated Lp(a)-hyperlipoproteinemia, in the prevention and progression of CVD. However, the majority of studies are observational (either retrospective or prospective). It is difficult to achieve ethical approval for RCTs assessing LA. However, a clinical trial currently underway (MultiSELECT – A European Multicenter Study on the effect of Lipoprotein(a) elimination by LA on cardiovascular outcomes) has circumvented this barrier by designing a study in which patients who receive LA in Germany are compared with matched patients elsewhere in Europe, in countries who do not offer reimbursed LA therapy [149]. Future studies such as these may provide stronger evidence for a role of LA therapy in the management of dyslipidemia and CVD.

Current FDA guidelines approve LA primarily for use in FH, and it is not a standard of care in the majority of patients with dyslipidemia in the United States. Countries including Germany and Japan are more advanced in terms of funding and availability of LA therapy, for patient populations outside of the FH subset. Obstacles include the time, cost, and difficulty some patients face accessing lipid apheresis centers in the United States. The development of new lipid-lowering therapy, particularly PCSK9 inhibitors including evolocumab, has caused debate as to whether these medications may be sufficient on their own to lower cholesterol levels and CVD risk. In 2017, a study by Hohenstein et al. [150] suggested that

only a small subset (10–12%) of patients receiving LA for elevated LDL in Germany may be able to stop LA and rely solely on PCSK9 inhibitors. Further studies are required to fully compare PCSK9 inhibitors to the efficacy of LA therapy. Of note, the additional benefits of LA therapy, aside from reduction of LDL and Lp(a) levels, are not present to the same extent with lipid-lowering therapy alone, and this should be considered when choosing a treatment option for a patient with hypercholesterolemia.

Conclusion

It is well established that elevated levels of LDL and/or Lp(a) are atherogenic and can promote the development and progression of CVD. Current therapies include first-line statin treatment, as well as adjunct therapies including ezetimibe and PCSK9 inhibitors. LA therapy is an additional treatment option to reduce cholesterol levels and remains a standard of care for patients with FH. The studies reviewed here indicate a beneficial role for LA therapy in the reduction of LDL and Lp(a) levels, as well as the reduction in ACVEs. Additional RCTs are required to strengthen the association between LA and CVD prevention. However, based on current evidence, LA therapy may be considered a safe, effective option for patients with hypercholesterolemia who are not responsive to standard lipid-lowering medication.

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