Arteriosclerosis, Thrombosis, and Vascular Biology

AHA SCIENTIFIC STATEMENT

Lipoprotein Apheresis: Utility, Outcomes, and Implementation in Clinical Practice: A Scientific Statement From the American Heart Association

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ABSTRACT: Despite the availability of multiple classes of lipoprotein-lowering medications, some high-risk patients have persistent hypercholesterolemia and may require nonpharmacologic therapy. Lipoprotein apheresis (LA) is a valuable but underused adjunctive therapeutic option for low-density lipoprotein cholesterol and lipoprotein(a) lowering, particularly in children and adults with familial hypercholesterolemia. In addition to lipid lowering, LA reduces serum levels of proinflammatory and prothrombotic factors, reduces blood viscosity, increases microvascular myocardial perfusion, and may provide beneficial effects on endothelial function. Multiple observational studies demonstrate strong evidence for improved cardiovascular outcomes with LA; however, use in the United States is limited to a fraction of its Food and Drug Administration–approved indications. In addition, there are limited data regarding LA benefit for refractory focal segmental glomerulosclerosis. In this scientific statement, we review the history of LA, mechanisms of action, cardiovascular and renal outcomes data, indications, and options for treatment.

Key Words: AHA Scientific Statements ■ blood component removal ■ cardiovascular diseases ■ cholesterol, LDL ■ familial hypercholesterolemia ■ glomerulosclerosis, focal segmental familial ■ lipoprotein(a) ■ secondary prevention

Hypercholesterolemia is a major risk factor for the development of atherosclerotic cardiovascular disease (ASCVD). Similar to pack-years of smoking, there is a dose–response relationship between the duration and severity of atherogenic lipoprotein particle elevation (low-density lipoprotein [LDL] cholesterol [LDL-C], non–high-density lipoprotein [non-HDL] cholesterol [non-HDL-C], remnant lipoproteins, and lipoprotein[a] [Lp(a)]) and ASCVD risk, sometimes referred to as LDL-years.[1] This relationship is notable in patients with familial hypercholesterolemia (FH), an autosomal codominant condition associated with severe LDL-C elevation from before birth, resulting in a greatly increased risk of ASCVD.[2] Despite multiple available therapies, patients with FH often require further reduction of LDL-C, for which lipoprotein apheresis (LA) can change the course of the disease process.

Lp(a) is an apoB (apolipoprotein B)–containing atherogenic lipoprotein that is associated with increased risk of ASCVD, arterial thrombosis, and calcific aortic stenosis (AS).[3] Lp(a) levels are elevated in ≈20% of individuals worldwide and in a greater percentage of individuals with FH, accentuating the already high risk of ASCVD attributable to FH.[4,5] A recent Mendelian randomization analysis illustrated an ≈6-fold increase in ASCVD risk in patients with elevated Lp(a) levels.[6] Highly efficacious options for lowering Lp(a) levels are limited, other than LA. Definitive proof of cardiovascular benefit of specific Lp(a)-targeted therapy is lacking, but indirect evidence suggests that lowering Lp(a) levels with LA is associated with decreased ASCVD risk.[7]

The devices listed here serve only to illustrate examples of these types of devices. This is not intended to be an endorsement of any commercial product, process, service, or enterprise by the American Heart Association.

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Aside from its role in treating LDL-C and Lp(a) elevation, LA is beneficial in reversing kidney disease in a portion of patients with refractory focal segmental glomerulosclerosis (FSGS) and may be beneficial in off-label treatment of preeclampsia. In this scientific statement on LA, we review the historical development, available devices, indications, efficacy, vascular effects, outcomes data, use in special populations, availability, access, cost, and patient perspectives. An informational handout about LA was developed for patient education. It is available in the Supplemental Material.

FH TREATMENT OPTIONS AND POTENTIAL INDICATIONS FOR LA

FH is among the most common genetic disorders of lipid metabolism worldwide, with a prevalence of ≈1:250 for heterozygous FH (HeFH) and 1:250 000 for homozygous FH (HoFH),[8] yet it remains substantially underdiagnosed and undertreated. Pathogenic loss-of-function variants in the gene encoding for the LDL receptor (LDLR) account for most cases of FH. Pathogenic variants in several other genes also decrease efficiency of LDLR-mediated hepatic clearance of LDL particles from the circulation, including loss-of-function variants in *APOB* (apoB), gain-of-function variants in *PCSK9* (proprotein convertase subtilisin:kexin type 9), and biallelic loss-of-function variants in *LDLRAP1* (LDL receptor adaptor protein 1).[9]

Adult patients with HeFH commonly have untreated LDL-C levels of 190 to 450 mg/dL (depending on mutation severity and other factors) in association with a 50% risk of an ASCVD event by age 50 years in men and 65 years in women if they remain untreated.[10] Pediatric and adult patients with HoFH commonly have untreated LDL-C levels of 450 to 1100 mg/dL, resulting in a mean age at first ASCVD event of 12 years and death at age 18 years, if untreated.[11] Although patients with HeFH generally achieve the expected magnitude of LDL-C reduction in response to standard, LDLR-based lipid-lowering pharmacotherapy, patients with HoFH have greatly reduced or no LDLR activity, and therefore an attenuated response to standard medications that lower LDL-C levels by increasing LDLR activity. Patients with HeFH and HoFH who have refractory hypercholesterolemia may be candidates for LA for both primary and secondary prevention.

Several guidelines recommend the need to lower LDL-C levels to <70 mg/dL in primary prevention and <55 mg/dL in secondary prevention in patients with FH. Whereas the European guidelines recommend an LDL-C level of <55 mg/dL, the 2018 American College of Cardiology/American Heart Association guidelines suggest an LDL-C level <70 mg/dL in secondary prevention. Nevertheless, the initial treatment goal is to achieve ≥50% reduction in LDL-C level from baseline.[12] However, registry data highlight that the majority of patients with FH do not achieve their risk-stratified LDL-C goals, leaving them with considerable residual risk.[13,14] The foundation of all lipid-lowering interventions is lifestyle modification. Statin therapy is the first pharmacologic choice for lowering LDL-C because of its proven safety, efficacy, and cost-effectiveness, but is rarely sufficient to achieve LDL-C goals in patients with HeFH, and never sufficient in HoFH. Guideline-based adjunctive treatment with ezetimibe, PCSK9 monoclonal antibodies, inclisiran, bile acid sequestrants, and bempedoic acid can facilitate additional LDL-C reduction, but LDL-C levels may remain above goal despite multidrug regimens, particularly in patients with HoFH. Two other drugs that function independently of LDLR are approved only for patients with HoFH. Lomitapide, a microsomal triglyceride transfer protein inhibitor, reduces hepatic production and secretion of very-low-density lipoproteins, which are obligate precursors to LDL; evinacumab, a monoclonal antibody against ANGPTL3 (angiopoietin-like protein 3), reduces formation of LDL by promoting clearance of very-low-density lipoproteins and intermediate-density lipoproteins through non–LDLR-dependent pathways. These medications are costly and have little or no data for ASCVD prevention. Despite mean LDL-C reduction of 20% to 40% with lomitapide, which is dose-dependent, and 49% with evinacumab, many patients with HoFH remain above the LDL-C goal, even with multidrug combination therapies,[15] and some may be limited by medication-associated side effects.[16,17] Liver transplantation is a rarely used invasive treatment for severe refractory HoFH.[18] Gene therapy for HoFH is in early stage clinical development.[19]

LA is efficacious for lowering all apoB-containing lipoproteins, including LDL-C and Lp(a), and is generally well tolerated. LA is approved worldwide for LDL or Lp(a) lowering, and is used more commonly in some countries (eg, Germany, United Kingdom) than in the United States. In the United States, LA is approved by the Food and Drug Administration (FDA) for patients with FH after lifestyle intervention and maximal tolerated LDL-C–lowering medications at differing LDL-C thresholds (Figure 1). Although reimbursement is decided individually by insurance carriers, it is expected that a patient will have exhausted other available evidence-based therapies as tolerated based on response and tolerability. LA is the only FDA-approved treatment for Lp(a) lowering, but only in patients with FH and LDL-C level >100 mg/dL. LA is also FDA-designated under a humanitarian device exemption for treatment of refractory primary FSGS.[20] Despite the indications and benefits of LA, it remains underused for high-risk patients with suboptimal lipoprotein control.

LA DEVELOPMENT, INDICATIONS, EFFICACY, AND EFFECTS

History of LA Development

The invention of the continuous flow centrifugal cell separator enabled plasma exchange to be performed

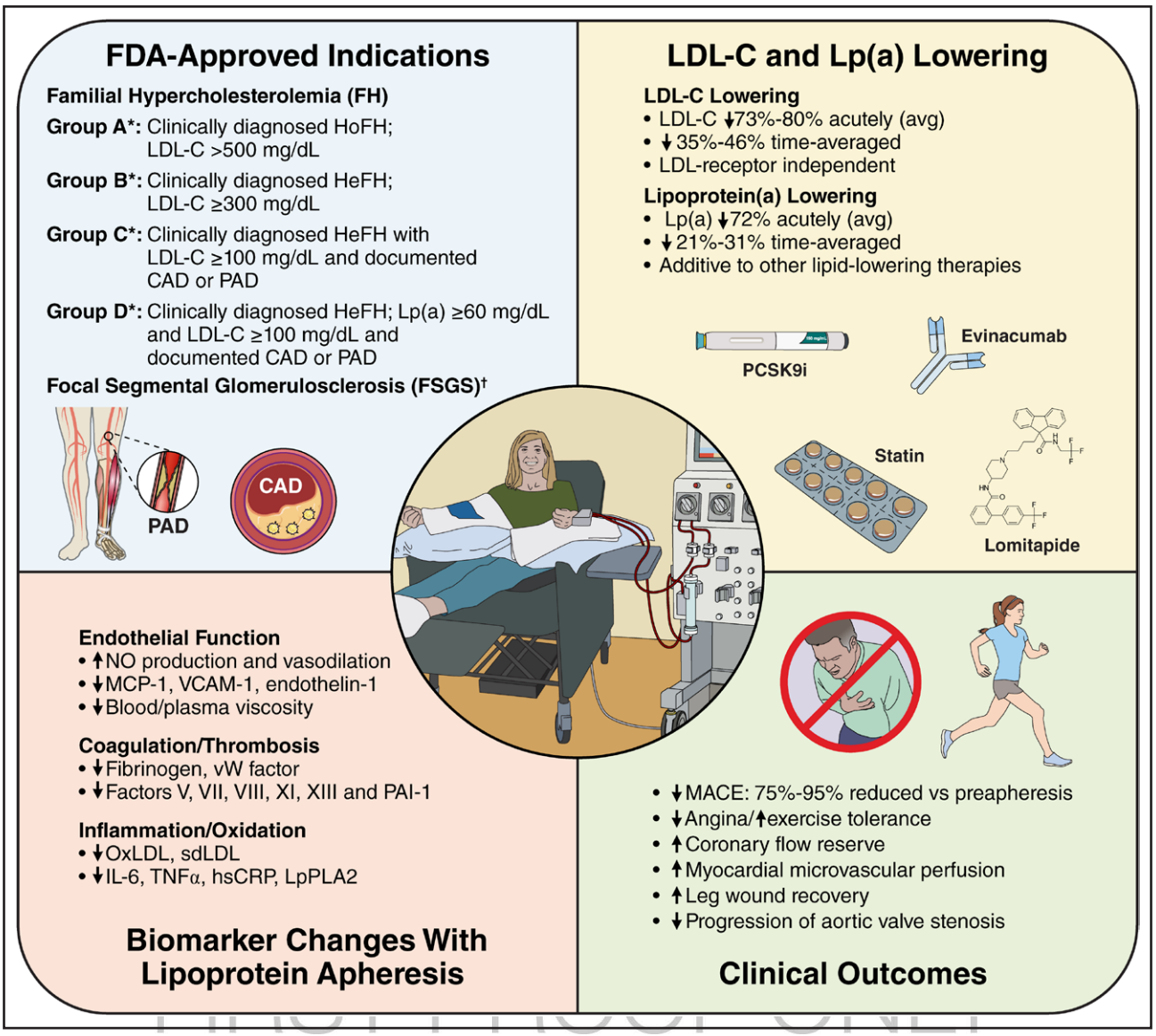

Figure 1. Lipoprotein apheresis: an overview of key concepts.
Food and Drug Administration (FDA)–approved indications are for patients with lifestyle intervention and maximal tolerable drug therapy who are unable to achieve appropriate low-density lipoprotein cholesterol (LDL-C) goals. Patients must meet 1 of 4 criteria (groups A–D) based on their clinical diagnosis of homozygous familial hypercholesterolemia (HoFH) or heterozygous familial hypercholesterolemia (HeFH), elevated LDL-C and lipoprotein(a) (Lp[a]) levels, and, for some, established coronary artery disease (CAD) or peripheral artery disease (PAD). Extent of expected LDL-C and Lp(a) reduction are summarized. Biomarker changes with lipoprotein apheresis and clinical outcomes are also outlined. hsCRP indicates high-sensitivity C-reactive protein; IL, interleukin; IMT, intima-media thickness; Lp-PLA2, lipoprotein-associated phospholipase A_2; MACE, major adverse coronary event; MCP-1, monocyte chemoattractant protein-1; NO, nitric oxide; OxLDL, oxidized low-density lipoprotein; PAI-1, plasminogen activator inhibitor 1; PCSK9i, proprotein convertase subtilisin:kexin type 9; sdLDL, small dense low-density lipoprotein; TNF, tumor necrosis factor; VCAM-1, vascular cell adhesion molecule 1; and vW, von Willebrand. *All on maximal tolerable lifestyle intervention and drug therapy. †Authorized by US federal law as a humanitarian use device.

successfully in 2 patients with HoFH in 1975.[21] However, plasma exchange has now been largely replaced by LA, which avoids exposure to heterologous blood products and removal of HDL. Selective removal of LDL particles using a cell separator to perfuse plasma through an immunoadsorbent column was introduced in 1981.[22] Because of subsequent work at the Rogosin Institute in partnership with Kaneka, this procedure was superseded by methods involving perfusion of anticoagulated plasma or blood through affinity columns containing either dextran sulfate (DS) covalently linked to cellulose beads (Figure 2) or polyacrylate-coated polyacrylamide beads, which adsorb the apoB component of LDL and Lp(a) and thus permit removal of these lipoproteins and their cargo of cholesterol (Figure 3) from the circulation.[23,26]

Other methods of LA involve extracorporeal precipitation of LDL by the addition of a heparin–acetate

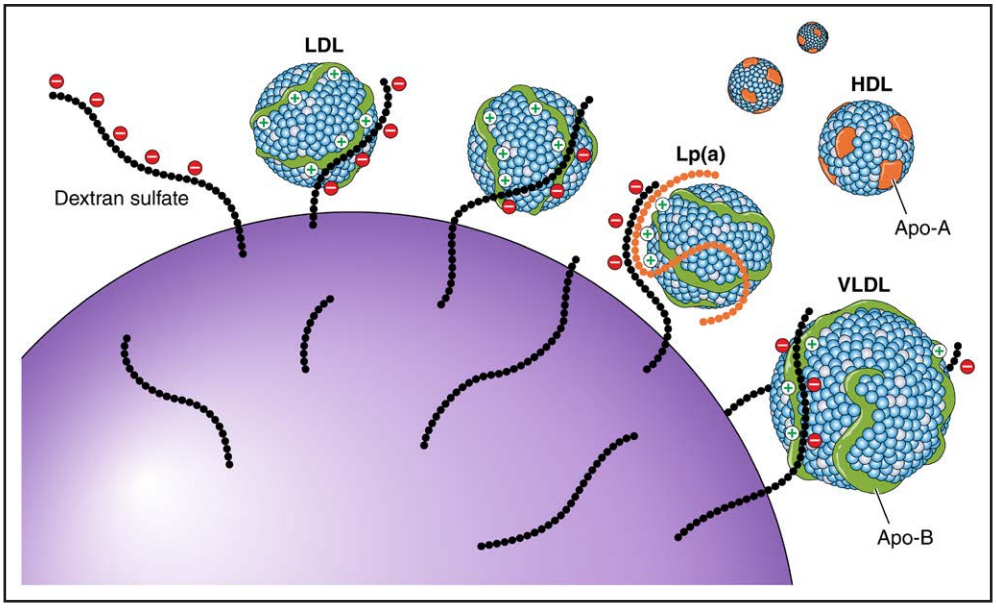

Figure 2. Schema of dextran sulfate cellulose beads.
Visualization of components that comprise dextran sulfate cellulose beads, including dextran sulfate, low-density lipoprotein (LDL), lipoprotein(a) (Lp[a]), high-density lipoprotein (HDL), very-low-density lipoprotein (VLDL), apoA (apolipoprotein A1), and apoB (apolipoprotein B).

buffer to plasma (heparin-induced extracorporeal LDL precipitation) and double-filtration plasmapheresis. The most popular methods used in the United Kingdom are DS adsorption and polyacrylate/polyacrylamide adsorption of apoB-containing lipoproteins from whole blood (hemoperfusion).[27] DS adsorption of plasma (but not hemoperfusion) and heparin-induced extracorporeal LDL precipitation are approved by the FDA, although the latter is no longer used in the United States.[28–30] Available LA procedures are summarized in Supplemental Table 1.

Indications for LA and Determinants of Efficacy

FDA-Approved Indications

The LIPOSORBER LA-15 system (Kaneka Pharma) is approved for patients with any of the following diagnoses in whom dietary intervention and maximum drug therapy has been either ineffective or not tolerated: HoFH with LDL-C level >500 mg/dL; HeFH with LDL-C level ≥300 mg/dL; or HeFH with LDL-C level ≥100 mg/dL, Lp(a) level ≥60 mg/dL, and documented coronary artery disease (CAD) or peripheral artery disease.[20]

The LDL-C thresholds for the indicated patient populations are results obtained after dietary and lifestyle intervention in combination with maximally tolerated combination drug therapy.[20] Documented CAD includes disease diagnosed by invasive or computed tomography coronary angiography, noncontrast computed tomography, or a history of myocardial infarction, percutaneous coronary intervention, or coronary artery bypass graft surgery. Documented peripheral artery disease includes disease diagnosed by symptoms or physical examination (eg, using the Rutherford classification), or both, ankle-brachial index, ultrasound examination, pulse volume recording, peripheral vascular angiography, or history of peripheral vascular intervention, peripheral vascular bypass surgery, or minor or major amputation. The indications for LA in different countries are detailed in Supplemental Table 2.[20,26,31–35]

LA Efficacy for LDL-C and Lp(a) Lowering

The magnitude of acute reduction in LDL-C levels after LA depends on the volume of plasma or whole blood treated. An acute decrease of up to 85% may be achieved by treating ≈2 plasma or blood volumes. Because LDL-C levels rebound quickly after LA, the more frequently the procedure is performed, the greater the reduction in time-averaged LDL-C levels.

The best estimate of the ensuing reduction in total or LDL-C levels is obtained by calculating the predicted interval mean value between successive procedures from the postapheresis LDL-C level achieved before the next preapheresis LDL-C level achieved.[36] The equation as devised by Kroon et al[37] is as follows: $C_{mean}=C_{min}+K(C_{max}-C_{min})$, where C_{min} is the cholesterol level immediately after an LA procedure, C_{max} is the cholesterol level at the start of the subsequent procedure, and K is the rebound coefficient (estimated to be 0.65 for patients with homozygous FH and 0.71 for patients with heterozygous FH receiving statin therapy and undergoing apheresis at biweekly intervals).[38] In an ideal scenario, 2 blood or plasma volumes are treated during each procedure, using a vein-to-vein approach and heparinized blood flow of 40 to 60 mL/min or more. When performed

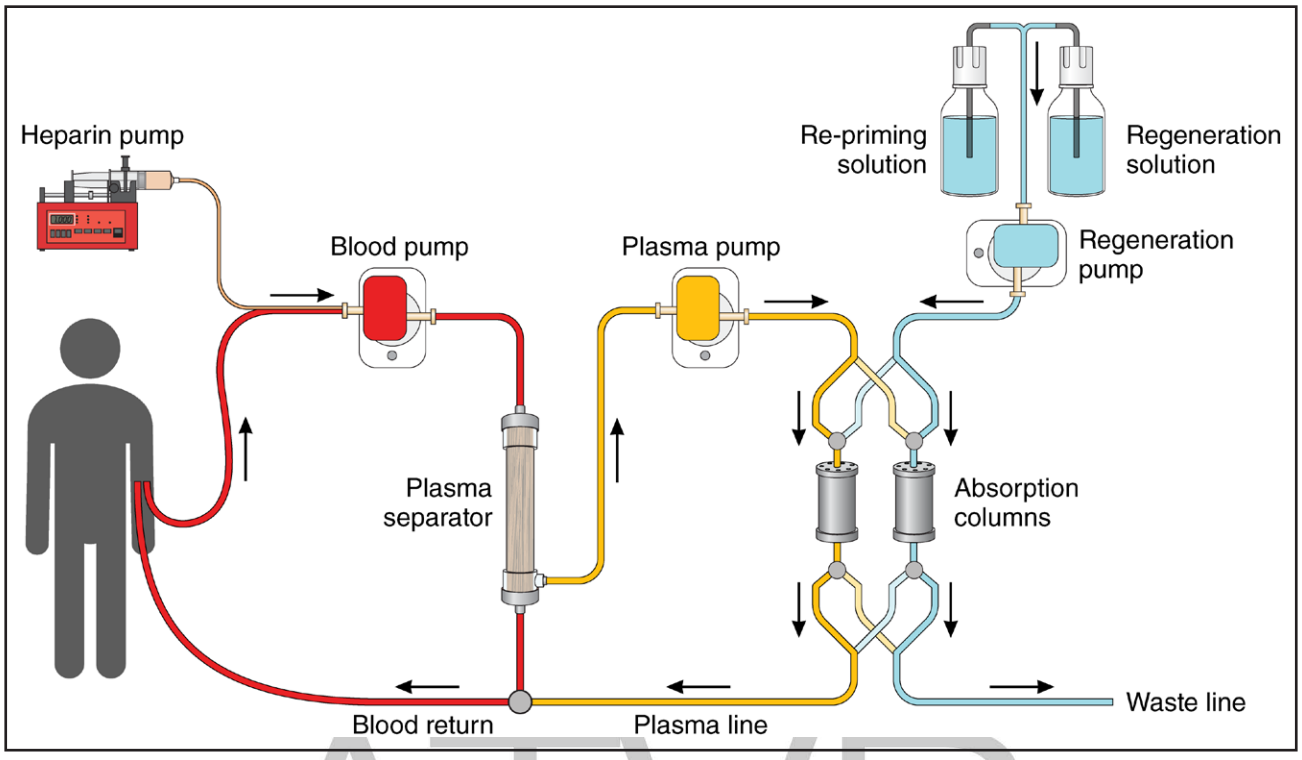

Figure 3. Dextran sulfate adsorption system.
Schematic for the removal process of plasma elements from the patient's blood through polyacrylate-coated polyacrylamide beads, which adsorb the apoB (apolipoprotein B) component of low-density lipoprotein (LDL) and lipoprotein(a) (Lp[a]), removing lipoproteins and cholesterol from circulation through apheresis. This process requires the separation of plasma from the red blood cells. Adapted from Gordon et al[23] with permission from Elsevier (Copyright © 2018 Elsevier); adapted from Moriarty and Hemphill[24] with permission from Elsevier (Copyright © 2015 Elsevier); and adapted from Moriarty[25] with permission of Elsevier Science & Technology Journals (Copyright © 2009); permission conveyed through Copyright Clearance Center, Inc.

every 2 weeks, mean time-averaged LDL-C reduction is ≈35% in patients with HoFH and 22% in patients with HeFH. Repeated at weekly intervals, the decreases from baseline in interval mean values of LDL-C are 46% in HoFH and 31% in HeFH; the mean decrease is greater in HoFH because of a slower LDL rebound attributable to a lower fractional LDL removal rate. Among patients with HoFH, treatment with weekly LA in combination with a multidrug LDL-C–lowering regimen may lower the time-averaged LDL-C concentration up to 70% to 80% compared with untreated baseline levels (Figure 4).[39] Expected reduction in Lp(a) levels with LA are similar to decreases in LDL-C levels.

Other Lipid and Vascular Effects Associated With LA

The most common LA devices (heparin-induced extracorporeal LDL precipitation, Liposorber, and Dali) remove apoB-containing lipoproteins on the basis of the positive isoelectric charge of apoB and may also remove other positively charged plasma proteins.

Improvement in a number of biomarkers and vascular function have been noted with LA, but whether these acute effects are directly linked to improved outcomes independent of lipoprotein lowering is unknown. With respect to endothelial function, nitric oxide production and vasodilation are increased; MCP-1 (monocyte chemoattractant protein-1), VCAM-1 (vascular cell adhesion molecule 1), and endothelin are reduced; and blood and plasma viscosity are reduced. With respect to coagulation and thrombosis, fibrinogen and von Willebrand factor are reduced, as well as factors V, VII, VIII, XI, XIII, and PAI-1 (plasminogen activator inhibitor 1). In terms of inflammatory and antioxidant effects, oxidized LDL and small dense LDL are reduced, as are interleukin-6, tumor necrosis factor–α, high-sensitivity C-reactive protein, and Lp-PLA$_2$ (lipoprotein-associated phospholipase A$_2$).[25]

High-Density Lipoprotein Cholesterol

Because of its negative isoelectric charge, only a small percentage of HDL particles is removed during LA, and HDL-C levels return to baseline within 1 to 2 days. Proteomic analyses have identified >80 proteins bound to HDL-C, such as positively charged apoE (apolipoprotein E), serum amyloid A, and apoCIII (apolipoprotein CIII), which are largely removed during LA.[40,41] All 3 of these HDL-bound proteins are associated with increased risk of CVD.[42,43] Recent studies have found that low HDL particle number and elevated apoCIII-bound HDL levels are associated with increased risk of calcific aortic valve stenosis.[44] The HDL particle concentration, which may be a better predictor of ASCVD risk than total HDL-C levels, is increased after LA.[45,46] The clinical implications

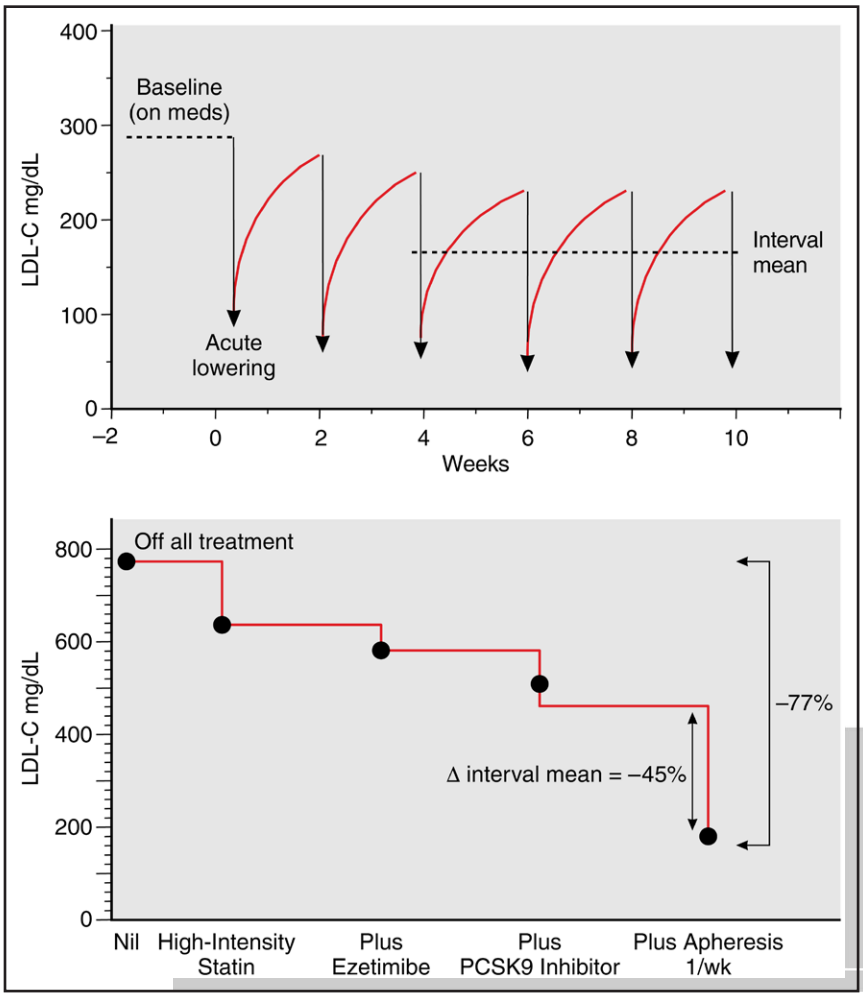

Figure 4. Assessment of the sequential contributions of a high-intensity statin, ezetimibe, evolocumab, and weekly lipoprotein apheresis to lowering low-density lipoprotein levels in a hypothetical familial hypercholesterolemia homozygote.
The upper graph exhibits the predicted interval mean value between successive procedures from the postapheresis low-density lipoprotein cholesterol (LDL-C) level achieved before the next pre–LDL-C level achieved. When performed every 2 weeks, mean LDL-C reduction between treatments is ≈35% in patients with homozygous familial hypercholesterolemia (HoFH). The lower graph demonstrates a reduction in time-averaged LDL-C concentration up to 70% to 80% compared with untreated baseline levels among patients with HoFH being treated weekly with lipoprotein apheresis, in combination with a multidrug LDL-C–lowering regimen. Adapted from Thompson.[39]

of changes in HDL composition, HDL-C, and HDL-P in response to LA are unknown.

Triglycerides

Acute reduction in triglycerides after LA is similar to cholesterol lowering, but triglycerides rebound to preapheresis levels in 24 hours, because turnover of very-low-density lipoproteins is much faster than that of LDL.[36] In patients with severe hypertriglyceridemia, LA is not a feasible option for lowering triglycerides, because chylomicrons obstruct the columns, limiting its use; however, plasma exchange (plasmapheresis) can be used in lieu of LA. Plasmapheresis in patients with triglyceride-induced pancreatitis, however, is controversial, and has unproven benefit.

Plasma Inflammatory Markers

LA reduces plasma markers of inflammation over both the short and long term in association with reduced markers of arterial inflammation, as noted in Table 1.[47–51]

Blood Rheology

Unlike plasma and water, blood is a non-Newtonian fluid in which shear stresses, red blood cell aggregation, red blood cell deformability, and plasma proteins can alter its resistance to flow. Increased blood viscosity is an independent risk factor for CVD and dementia. Both blood viscosity and red blood cell aggregation and deformability are substantially decreased after LA,[51,53] but whether these changes contribute to antiatherosclerotic or potential antithrombotic effects of LA is unknown.

Extravascular Cholesterol Deposits

Severe lifelong plasma LDL-C elevation in patients with FH contributes to progressive formation of often disfiguring subcutaneous and extensor tendon xanthomas, frequently occurring in Achilles tendons, sometimes limiting ankle mobility. Regression of xanthomas occurs slowly over months to years when the LDL-C concentration is substantially reduced. There is a rough correlation between severity of extensor tendon xanthoma volume and arterial plaque volume; therefore, decreases in severity of cutaneous and tendinous xanthomas during treatment with LA may correlate with a decrease in noncalcified arterial plaque.[39] Corneal arcus, consisting of precipitated LDL lipids and apoB in the peripheral corneal stroma, is poorly mobilized and typically is unchanged by LA because of the relatively avascular composition of corneal tissue.

Table 1. Proinflammatory Markers: Percent Changes After Lipoprotein Apheresis[47–51]

Marker	After apheresis, %
MCP-1	−15 to −18
MMP-9	−20
TIMP-1	−30
ET-1	−15 to −75
sCD40L	−16
Lp-PLA_2	−22
VCAM-1	−10 to −20
ICAM-1	−10 to −16
E-selectin	−6 to −31
Fibrinogen	−10 to −65
MPO	−36
SAA	−84
hsCRP	−10 to −80
Galactin-3	−19 to −23
IL-6	−35

ET-1 indicates endothelin-1; hsCRP, high-sensitivity C-reactive protein; ICAM-1, intercellular adhesion molecule-1; IL-6, interleukin-6; Lp-PLA_2, lipoprotein-associated phospholipase A2; MCP-1, monocyte chemoattractant protein-1; MMP-9, matrix metalloproteinase-9; MPO, myeloperoxidase; SAA, serum amyloid A; sCD40L, soluble CD40 ligand; TIMP-1, tissue inhibitor of metalloproteinase-1; and VCAM-1, vascular cellular adhesion molecule-1.

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LA AND ASCVD OUTCOMES

The majority of ASCVD outcome data related to LA are from prospective and retrospective observational studies. The absence of randomized placebo-controlled ASCVD outcomes trials of LA stems from the need for a sham procedure as well as ethical concerns about withholding a therapy that has evidence for improved outcomes in a high-risk population[54] with few other available therapies.

Data from uncontrolled studies that assessed ASCVD event rates after LA compared with before LA suggested that event rates are 50% to 85% lower after LA. These notable benefits may result from both lipid and nonlipid mechanisms, as described previously. Most of these studies used major adverse cardiovascular events (MACEs) as a primary end point and involved multiple cohorts in relatively diverse populations and regions, including Germany, Japan, the United States, and other European countries (Table 2).[27,54–63] Although mainly observational, the strength of this evidence derives from several factors, including the use of individuals as their own (historical) controls, the consistency of ASCVD benefits across multiple populations and many years of follow-up, as well as extensive supportive, mechanistic data.

The most notable cardiovascular outcome data are from an early nonrandomized parallel treatment trial assessing 10-year outcomes in 130 Japanese patients with HeFH with angiographically documented CAD treated with cholesterol-lowering drug therapy alone (n=87) or LA in combination with cholesterol-lowering drugs (n=43) over a mean duration of 6 years. LA in combination with drug therapy significantly reduced LDL-C levels, from 286.93±66.9 to 121.04±30.94 mg/dL (58%), compared with drug therapy alone, decreasing from 233.2±51.04 to 167.05±59.16 mg/dL (28%). Coronary event rates were 72% lower with combination therapy compared with drug therapy alone (10% versus 36%, respectively; *P*=0.0088; Figure 5).[54]

A subsequent retrospective longitudinal cohort study by Heigl et al[64] in 2015 compared 4 different types of LA methods among 118 patients with CVD and elevated LDL-C or Lp(a) levels. During a mean duration of 6.8 years of apheresis, the incidence of MACEs was 79.7% lower compared with a mean period of 6.4 years before apheresis. In 2022, the most recent update from a large multicenter prospective GLAR study (German Lipoprotein Apheresis Registry), by Schettler et al,[61] examined outcomes in 2028 patients with elevated LDL-C or Lp(a) levels, or both. A comparison of ASCVD event rates during 5 years of LA with the interval 1 to 2 years before LA showed a 74% lower occurrence of MACEs and 66% lower rate of major noncoronary events. Major noncoronary events were defined by the authors as a new transient ischemic attack, minor stroke or stroke, new carotid surgery, new carotid percutaneous transluminal angioplasty, or new peripheral vascular events (a vascular event of thoracic AS, lower extremities, or renal arteries with percutaneous transluminal angioplasty, stent, bypass surgery, or amputation). The relative risk reduction for MACEs in patients with Lp(a) elevation plus elevated LDL-C levels ranged between 60% and 90%, and the most recent GLAR data show 85% and 63% lower rates of MACEs and major noncoronary events, respectively. The ASCVD benefit from LA appeared to be greatest in patients with elevated Lp(a) and normal LDL-C levels, associated with relative risk reduction for MACEs and noncoronary events of 88% and 73%, respectively. Although 6 different LA methods were used in the GLAR study (DS and 5 others), the reports state that there was no difference in MACEs or major adverse noncoronary events reduction among these methods. Furthermore, although LA is commonly done weekly in Germany and Austria, and LA is commonly done every 2 weeks in the United States, United Kingdom, and Japan, the ASCVD relative risk reductions were roughly comparable.

In 2013, Leebmann et al[65] conducted a prospective multicenter study (Pro[a]LiFe) in 170 patients with Lp(a) elevation treated with LA. Annualized MACE rates during 2 years before and 2 years after initiation of LA were noted to be 0.41±0.45 versus 0.09±0.22, respectively

Table 2. Published ASCVD Event Outcomes With Lipoprotein Apheresis[27,54–63]

Country and publication	Type of study	No.	Sites	Dyslipidemia types (and comments)	ASCVD events (follow-up duration)
Japan					
Mabuchi et al (1998)[54]	Prospective/ nonrandomized, semimatched controls, unblinded evaluation	43 (vs 87 controls on medication only)	Japan/multi-center	HeFH with CAD	MACE ↓72% (P<0.01; controls vs LA; 6-y follow-up); controls generally well-matched to patients receiving LA, except 28% vs 9% smokers (P=0.02) and Achilles tendon thickness 12 vs 17 mm (P<0.001)
Masaki et al (2005)[55]	Prospective/ observational	18	Japan/single-center	HeFH (baseline LDL-C level 277 mg/dL)	MACE ↓95% (follow-up 0.9 y before LA vs 9.8 y on LA)
United States					
Gordon (2000)[56]	Retrospective/ observational	62	United States/multi-center	High LDL-C level	MACE ↓59% (P=0.037; 5 y before LA vs 4 y on LA)
Sachais et al (2005)[57]	Retrospective/ observational	34	United States/ single-center	High LDL-C level, n=33; high Lp(a) level, n=1	MACE ↓73% (follow-up before LA ND vs average 2.5 y on LA)
Moriarty et al (2019)[58]	Retrospective/ observational	14	United States/ single-center	Isolated high Lp(a) level; patients with high LDL-C level excluded	MACE ↓94% (6 y before LA vs 4 y on LA)
Germany					
Koziolek et al (2010)[59]	Retrospective/ observational	38	Germany/ single-center	High LDL-C level alone, 47%; high Lp(a) level alone, 5%; both elevated, 47%; events not reported by baseline lipids	MACE ↓83% (3 y before LA vs 9 y on LA)
Rosada et al (2014)[60]	Retrospective/ observational	37	Germany/ single-center	Isolated high Lp(a) level (patients with high LDL-C level excluded)	MACE ↓94% (P<0.0001; 1 y before LA vs 6.8 y on LA)
Schettler et al (2022)[61]	Retrospective/ observational	930	Germany/ multicenter	3 patient groups: (A) high LDL-C and normal Lp(a) level, (B) normal LDL-C and high Lp(a) level, and (C) high LDL-C and high Lp(a) level; includes Pro(a)LiFe and other previous, smaller published German studies; LA generally done weekly	MACE* ↓2 y before LA vs on LA 2 y (and on LA 5–7 y+) by group: (A) MACE ↓52% (↓74%), (B) MACE ↓85% (↓88%), (C) MACE ↓75% (↓85%)
Other European countries					
Sampietro et al (2015)[62]	Retrospective/ observational	30	Italy/single-center	All patients had HeFH or FCH (57% and 43%, respectively); 53% also had high Lp(a) level; events not reported by baseline lipid levels	MACE ↓88% (rate/y; follow-up 11 y before LA vs ≈15 y on LA)
Berent et al (2019)[63]	Retrospective/ observational	30	Austria/ single-center	50% with high LDL-C level only, 50% with high Lp(a) level; events not reported by baseline lipids; LA done weekly	MACE ↓78% (2 y before LA vs 2 y on LA)
Pottle et al (2019)[27]	Retrospective/ observational	151	United Kingdom/ multicenter	92% with high LDL-C only, 8% with high Lp(a)	MACE ↓63% (2 y before LA vs 2 y on LA)

Lipoprotein apheresis (LA) was performed every 2 weeks unless otherwise noted. ASCVD indicates atherosclerotic cardiovascular disease; FCH, familial combined hypercholesterolemia; HeFH, heterozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); and ND, no data.

*Major adverse cardiovascular events (MACEs) did not include stroke in this publication.

(78% reduction; P<0.0001). In another study, Schatz et al[66] showed in 2017 that in 113 patients with either elevated LDL-C >100 mg/dL, elevated Lp(a) >60 mg/dL, or both, the group with elevated Lp(a) level had the highest baseline MACE rate during 2 years before apheresis (1.57±1.31 for Lp[a] >60 mg/dL versus 0.59±0.63 for LDL-C >100 mg/dL) and the greatest relative decrease in events during 2 years of LA (77%, 74%, and 53% lower incidence of MACEs with high Lp[a] level, high Lp[a]+high LDL-C level, and high LDL-C level, respectively). In a post hoc analysis of another retrospective study of 133 patients treated with a statin, patients in the United Kingdom compared with patients in South Africa were more likely to be treated with LA (50% versus 13%, respectively), achieved greater serum cholesterol lowering (57% versus 32%), and had lower mortality rates (10% versus 60%; P=0.02) during 25 years of follow-up.[67]

KNOWLEDGE GAPS

Based on the observational nature of the existing data related to LA, there are important limitations to acknowledge. The studies are small and not randomized. It is

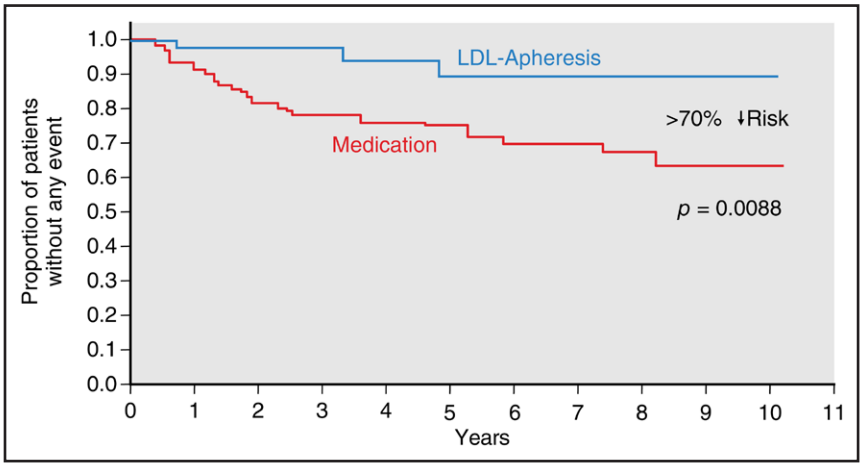

Figure 5. Reduction of cardiovascular events with low-density lipoprotein apheresis compared with drug therapy alone.
Outcome data of the Hokuriku-FH-LDL-Apheresis Study Group[54] demonstrating that among patients with heterozygous familial hypercholesterolemia (FH) with congenital heart disease documented by coronary angiography, the rate of total coronary events was 72% lower in the low-density lipoprotein (LDL) apheresis group (combined with cholesterol-lowering drugs) compared with those receiving drug therapy alone. Adapted from Moriarty and Hemphill[24] with permission from Elsevier (Copyright © 2015 Elsevier).

challenging to control for confounders in these populations, which may affect outcomes. Further research that may include randomized controlled trials or larger prospective studies is warranted to further substantiate the outcomes. There is also a need for expansion of research on the patient level with respect to patient experience and quality of life (QoL).

Plaque Regression

Smaller studies have examined the effects of LDL or Lp(a) reduction, or both, with LA on the end point of angiographically quantified coronary arterial plaque regression in patients undergoing LA, demonstrating decreased mean stenosis in response to either LDL or Lp(a) reduction, or both. The LACMART prospective Japanese study (Low Density Lipoprotein-Apheresis Coronary Morphology and Reserve Trial) of 17 patients with FH assigned to statin treatment versus statin treatment+LA noted a reduction in minimal lumen diameter in the statin+LA group compared with an increase in the statin alone group (minimal lumen diameter 0.12±0.43 mm with statin+LA versus −0.08±0.45 mm with statin alone; $P<0.004$).[68] Among 30 patients with elevated Lp(a) >50 mg/dL assigned to receive specific Lp(a) apheresis versus atorvastatin alone for 18 months, Safarova et al[69] showed a 2% reduction in mean luminal stenosis with LA compared with an increase of 3.5% in the atorvastatin alone group.

Myocardial Microperfusion

Decreased angina has been demonstrated in patients with refractory angina after treatment with LA. In 2017, Khan et al[70] randomized 20 patients to LA or sham apheresis, and then crossed over each participant to the other arm, each for 3-month periods. In addition to the expected reductions in LDL-C and Lp(a) levels, there was a noteworthy net increase of 0.63 in myocardial perfusion reserve ($P<0.001$), a 17% (67 meters) net increase in 6-minute walk distance ($P<0.001$), and improvement in several other measures with LA versus sham treatment.[70] In another trial, myocardial microvascular perfusion improved and was normalized when measured immediately after LA compared with immediately before LA.[71]

Lower-Extremity ASCVD

LA treatment is beneficial for patients with lower-extremity ASCVD, a condition associated with historically poor guideline-directed treatment uptake and poor clinical outcomes. A small registry of patients with lower-extremity ASCVD reported improvements in mean claudication levels, walking distance, ankle-brachial index, and revascularization rates (all $P<0.001$) before versus after starting once-weekly LA, with patients serving as their own (historical) controls.[72] Data from other studies have also shown improved endothelium-dependent vasodilatation and results from case series have demonstrated improved wound healing in patients with intractable skin ulcers caused by peripheral artery occlusion with the use of LA, particularly in the setting of elevated Lp(a) levels.[73]

AS (Valvular and Supravalvular)

Valvular and supravalvular AS are known complications of both FH and elevated Lp(a) levels,[15] yet few studies have assessed the effects of LA on AS. Data from a 50-year survey of UK patients suggested that LA in combination with statin therapy was associated with decreased incidence of AS compared with the prestatin era (33% versus 77%, respectively; $P=0.02$). Statin therapy alone has been ineffective for altering the course of AS. In addition, a study from France showed that later initiation of LA treatment in children with homozygous FH was associated with greater development of AS.[74] Although high Lp(a) levels are known to associate with calcific AS, published evidence of potential LA benefits on AS in patients with elevated Lp(a) levels are lacking.

Pediatric LA

The diagnosis of HoFH can be made early in childhood in the presence of cutaneous xanthomas and extremely high LDL-C levels.[75–77] Children with HoFH may have little or no LDL-C–lowering response to standard LDLR-dependent therapies, and LA or the LDLR-independent agents (or both) lomitapide and evinacumab are often needed to achieve goal LDL-C levels of <115 mg/dL.[15] Without aggressive LDL-C reduction, atherosclerosis often develops rapidly, and myocardial infarction and sudden death may manifest by the second decade, and at times even in early childhood.[75–77] Aggressive LDL-C–lowering therapy is needed as soon as a diagnosis of HoFH is established because a delay of even 3 to 6 months may lead to ASCVD complications.

LA is generally safe and effective for lowering LDL levels in patients with HoFH as young as 2 years.[35,75,76] Treatment of ≈1.5 plasma volumes (lower than the goal of 2 volumes in adults) over 2 to 3 hours every 1 to 2 weeks with DS adsorption achieves similar acute and time-averaged lowering of LDL-C and Lp(a) levels as reported for adults.[76,78] Serious adverse events are rare, but a minimum body weight of 15 kg is recommended because of the large extracorporeal volume (≈400 mL for Liposorber) and potential for hypotension. The risk of hypotension can be limited by pre-LA volume expansion with oral hydration; possible infusion of 25% albumin during the initial removal of blood (to compensate for decreased blood volume); a slow initial blood flow rate, gradually increased as tolerated; and boluses of normal saline as needed.[78] It is important to assess the aortic valve/root area and patency of the coronary arteries before starting LA because of the enhanced risk of hypotension and myocardial ischemia. The safest venous access is by peripheral venipuncture, but this can be difficult in children because of small venous caliber and frequent lack of cooperation with needle insertion and catheter placement maintenance. Subdermal placement of a central port is possible, even in young children, and can be valuable in providing a reliable source of blood withdrawal, to be complemented by blood return through a peripheral vein. Skilled and sensitive engagement with the child and parent are needed. Venous access complications are more common in children compared with adults.[79]

The earlier patients with HoFH begin treatment with LA and the lower their on-treatment LDL-C levels, the better their cardiovascular event–free survival rates.[76,77,80,81] Cutaneous and aortic valvular xanthomas, as well as plaque in the coronary arteries and aorta, may regress, but if the LDL-C concentration remains above goal, ASCVD events may occur.[75,76,78] Children with HoFH and elevated Lp(a) levels may especially benefit from LA. Children with high Lp(a) levels and stroke may also benefit from LA.[82] Larger studies in pediatric patients with HoFH are needed to better quantify the ASCVD benefits of LA when used in combination with aggressive medical therapy.[83]

LA and Pregnancy

Treatment of lipid disorders is particularly challenging during pregnancy and lactation, because increased estrogen levels elevate both LDL-C and triglyceride levels.[84] LDL-C levels are further elevated by the need to stop most pharmacotherapies during pregnancy and lactation, other than bile-acid sequestrants and possibly statins.[85] Although there are no published clinical trials of LA in pregnancy, results from case series attest to LA being safe and effective for lowering LDL-C in women with severe ASCVD or familial hypercholesterolemia, or both, throughout pregnancy and breastfeeding.[10,86] Careful assessment of cardiovascular stability is needed in women who have experienced a recent ASCVD event to ensure safety for both the mother and fetus, as well as to assess the potentially high risk of cardiovascular complications due to not performing LA. Severely elevated LDL-C and possibly Lp(a) levels can be deleterious to both the mother and fetus, leading to risk for maternal cardiac events, preterm birth, preeclampsia, and death from myocardial infarction during parturition in women with HoFH who stop all lipid-lowering treatment during pregnancy.[87] Preliminary results suggest that off-label treatment with LA may reduce the likelihood and severity of preterm preeclampsia.[88,89]

LA for FSGS

Nephrotic syndrome is characterized by excessive urinary protein excretion, usually associated with mild to severe dyslipidemia (elevated LDL-C level, elevated Lp[a] level, hypertriglyceridemia, and low HDL-C level), often with a reduced glomerular filtration rate (GFR). An important cause of nephrotic syndrome is primary FSGS, which is treated with glucocorticoids and calcineurin inhibitors. Patients who are unresponsive to these treatments are candidates for renal transplantation. FSGS often recurs in the renal allograft and may be unresponsive to immunosuppressive medications. Cases of recurrent FSGS can be treated with plasma exchange (also known as plasmapheresis), although this often provides little or no benefit, perhaps because it is relatively inefficient in removing the underlying circulating factors that may contribute to primary FSGS.[90] Published data implicate several potential aggravating factors in FSGS, which may include remnant lipoproteins, other lipoproteins, apolipoprotein L1, and many other proteins and apoproteins suggested by proteomic analyses.[91]

In the 1980s, given evidence that dyslipidemia is associated with FSGS, LA was first used for treatment of this condition, and found to be potentially effective for some patients with FSGS. Use of LA for refractory FSGS (definite or presumed) has been reported in at least 17 publications of adult patients (with 1–29 patients each), totaling ≈141 unique participants. Most patients (n=119) were in the 6 largest studies (13–29 participants each),

including 1 RCT of statin treatment with or without LA.[92–95] Major limitations of these data are the inclusion of 20 RCT participants for nephrotic syndrome (not specifically FSGS) and use of the primary outcome of LDL-C lowering (which was better with LA) rather than severity of proteinuria (which trended lower with LA) or effect on GFR (which was not reported).[92] Of the remaining 99 (observational) patients, 46% had complete proteinuria remission, 30% achieved partial remission, and 25% had little or no benefit. Renal function normalized in 58%, 28% had partial improvement, and 15% had no improvement.

A potential benefit of LA in pediatric patients (age 2–18 years) with FSGS was reported in 11 publications (1–11 cases each), totaling 40 unique patients.[96] The response to LA in children appears to be somewhat better than in adults, but there are many potentially confounding differences between these publications. For the outcome of proteinuria, ≈58% had complete remission, 15% partial benefit, and 27% little or no benefit. GFR was normalized or remained normal in 77%; 23% had no benefit.

Substantial limitations of the available data include (1) a near-total lack of RCTs or nonrandomized control groups; (2) wide variability in treatment protocols; (3) underreporting of renal (and lipid) outcomes; (4) variable and often brief follow-up (1 month to 12 years); (5) large losses to follow-up (half or more in some series); (6) lack of published meta-analyses or systematic reviews; and (7) considerable likelihood of publication bias. Further clinical studies of LA treatment in adults and children with FSGS are needed, including both systematized registry data and RCTs (eg, LA versus plasma exchange), focusing on the major renal outcomes of proteinuria and GFR. Studies focused on mechanisms of benefit and biochemical predictors of response are also needed.

LA improves renal function in some patients with FSGS, even in patients with medication resistance and relapse. Predictors of greater benefit include younger age, concurrent use of glucocorticoids, shorter duration of FSGS, and better baseline renal function. The FDA has approved LA under a humanitarian device exemption for treatment of adults and children with primary FSGS and nephrotic syndrome that is resistant to corticosteroids or calcineurin inhibitors (or both), or recurrent after renal transplant, with a GFR ≥45 mL·min·1.73 m^2 (although the response is better with GFR ≥60). Although the FDA's semiexperimental humanitarian device exemption designation of LA for FSGS reflects the lack of documented consistent clinical benefit, LA is routinely approved for FSGS by most payers. Institutional review board oversight and approval as an exempt experimental treatment is required for centers that use LA for treatment of FSGS. The recommended short course of LA (usually twice weekly for 3 weeks, then once weekly for 6 weeks, for a total of 12 treatments over 9 weeks) in some cases results in long-term remission of a serious and otherwise untreatable disease.

PUTTING LA INTO PRACTICE

Availability of LA Centers

Although some countries, such as Germany, have widespread LA centers with high patient capacity, other countries have limited or no availability of LA. In the United States, the closest LA center may be >300 to 400 miles away for some patients. It is estimated that up to 1% of patients with FH in the United States may qualify for LA (a modern estimate adapted from Vishwanath and Hemphill [2014][97]), which may comprise 11 000 to 15 000 patients. This is >25 times the <400 US patients reported by Kaneka Medical Company to be undergoing LA, underscoring the barriers to access and likely lack of awareness of its benefits and indications. In accordance, there is a need for more referrals to existing LA centers, as well as creation of more LA centers to make the procedure more accessible. An up-to-date listing of active LA sites can be found on the Family Heart Foundation website.[98] Underdiagnosis of FH and high Lp(a) level is an additional barrier to treatment with LA.

Requirements to Establish an LA Center

The requirements for establishing an LA center are relatively straightforward (Figure 6). Key components include availability of trained nursing staff with backup, adequate space with a hospital bed or reclining chair for performing LA treatments, an LA device and disposable supplies (only the Liposorber system is available in the United States), as well as referral of appropriately indicated patients. Nurses who are experienced with dialysis or other apheresis procedures can more readily be trained to perform LA, but the needed training specific to LA is available and is feasible for most RNs. Apheresis devices can be purchased or leased from the manufacturer or distributor. Tubing, plasma separators, and apheresis columns are for 1-time use.

When a patient is identified who may be a candidate for LA, the next steps include verification that available pharmacotherapeutic options have been attempted; documentation that the patient meets approved criteria from the FDA in the United States or other regulatory bodies in other countries (Table 2)[26,51,53–61]; careful discussion with the patient of pros and cons of the procedure, including potential risks and costs; obtaining authorization from the patient's insurance plan; and assessment of venous access. LA is covered by most insurance plans, although reimbursement rates vary by state and plan. In the United States, a company that partners with Kaneka offers free expert assistance in obtaining insurance authorization.[99]

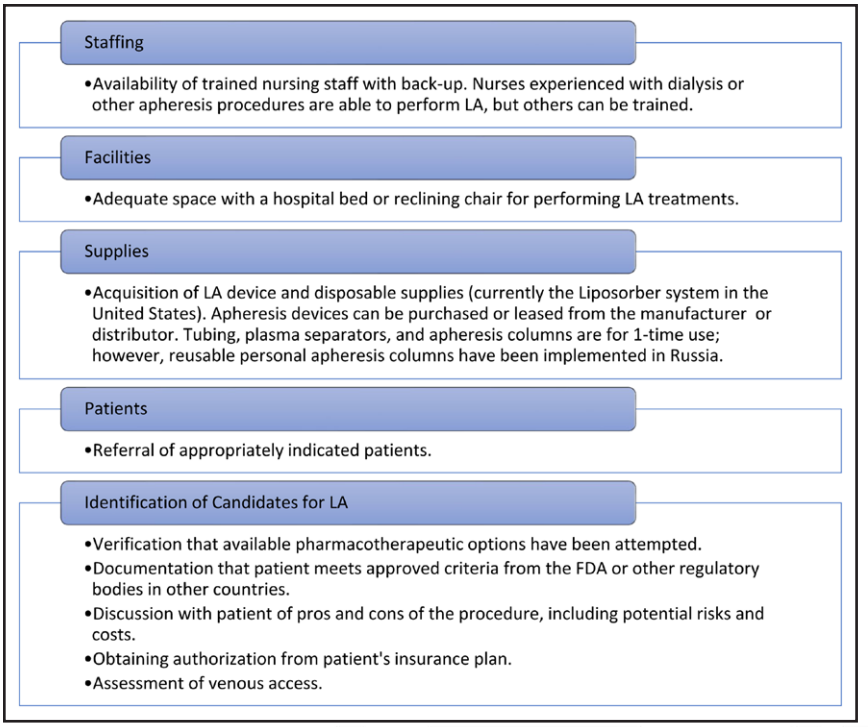

Figure 6. Establishing a lipoprotein apheresis center.
Outline of the key components necessary for establishing a lipoprotein apheresis (LA) center. Elements addressed include staffing, facilities, supplies, identification, and referral of appropriately indicated patients. FDA indicates Food and Drug Administration.

Administrative support for implementing and maintaining an LA center is essential. Unfamiliarity with the process and procedure may create initial administrative hesitancy in some cases, but detailed discussions of the unique unmet needs of high-risk patients with severe FH or Lp(a) elevation (or both), in addition to the benefits of LA for such patients, may help overcome these barriers. A detailed financial plan is required, which can be negotiated in coordination with the apheresis device provider, to verify that a sustainably viable program can be initiated. It has been estimated that a center with 2 or 3 patients treated with regular LA will yield financial neutrality for the institution. Because many health care professionals are unaware of LA, selective marketing can facilitate identification of patients who may be candidates for this procedure. For institutions that are not prepared to train their staff to support the procedure or to purchase or lease an LA machine, local blood centers and companies may provide mobile LA service in limited areas on an ongoing basis, with nurses and an apheresis device brought to the required site weekly or biweekly. More information about local resources can be obtained from Kaneka.[99] In cases where an LA center might be run by a nephrologist or blood bank specialist, availability of a qualified lipidologist is needed for appropriate management of lipid-lowering medications and care of patients receiving LA, who are at high risk for ASCVD events.

Venous Access

Some patients can sustainably undergo LA treatments using their native veins for afferent and efferent blood access. In adults, this generally requires 16- or 18-gauge venous access in both arms to provide adequate blood flow rates; lower flow rates prolong treatment times. When native venous access is insufficient, alternative options include implantation of subdermal high-flow central venous ports accessible in the upper chest (eg, Bard or Vortex), use of a dual-lumen transcutaneous tunneled central venous dialysis catheter (generally only for temporary use), or surgical creation of an arteriovenous fistula in the forearm, which may require 6 to 8 weeks to mature before use for LA. The best option for each patient needs to be identified on the basis of shared decision-making and a well-informed understanding of the pros and cons of each option. Central lines can increase risk of infection and sepsis, particularly in children. Central lines and ports require flushes with heparin in between treatments if not used regularly for LA. Percutaneous central lines generally require at least weekly flushes, necessitating flushes between every 2-week LA treatment. Arteriovenous fistulas do not require flushing but may be cosmetically undesirable and may pose risk of bleeding from the arterialized pressurized dilated vein in patients at risk of forearm trauma.

Cost-Effectiveness of DS LA for Prevention of ASCVD

The annual cost of LA varies greatly by setting (outpatient versus hospital), by payer (Medicare, Medicaid, or commercial insurer), and by region, ranging from $50 000 to $150 000 per year in the United States when performed at the common interval of every 2 weeks. Although

substantially more costly than the most expensive LDLR-dependent LDL-lowering therapies, LA is substantially less expensive than the only other available treatments for patients who fail these therapies, because the 2 LDLR-independent medications for HoFH, lomitapide and evinacumab, cost ≈$300 000 to $450 000 annually (both approved as orphan drugs for patients with HoFH). Neither of these medications has reliable data for ASCVD event reduction. LA is the only FDA-approved treatment for high Lp(a) levels in patients with FH and LDL-C >100 mg/dL taking standard LDL-C–lowering therapy.

An estimate of the cost-effectiveness of LA for ASCVD event reduction can be made by comparing results of the most comprehensive study of ASCVD outcomes in patients treated with LA[61] with that of the largest ASCVD outcomes trial of evolocumab, the most commonly used PCSK9 inhibitor.[100] The most recently published cost-effectiveness calculations for evolocumab[101] showed cost-effectiveness "below the threshold of $50 000 per quality-adjusted life-year gained for any baseline [ASCVD event] rate of ≥6.9 events per 100 patient-years." The average reduction rate for LA for all major ASCVD events (coronary plus noncoronary) in the GLAR[61] was 5.2%, compared with 1.5% with evolocumab in FOURIER (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk), which had a primary outcome of nonfatal myocardial infarction and stroke and cardiovascular disease death.[100] These 2 studies tested both a comparable on-treatment period (2 years for the primary analysis in the GLAR versus 2.2 years median follow-up in FOURIER) and a comparable baseline ASCVD risk (7.35% in GLAR versus the "very-high-risk" subgroup in FOURIER ["6.9% or more"]). Thus, LA may provide a 3.8-fold greater ASCVD risk reduction than evolocumab. Assuming an annual discounted cost of $50 000 for LA versus an annual discounted cost of $6634 for evolocumab (lowest cash price for a national pharmacy chain[102]), LA costs roughly 7.6-fold more than evolocumab. Because the 7.6-fold extra cost is roughly twice that of the 3.8-fold extra ASCVD risk reduction, it is reasonable to estimate that the cost-effectiveness of LA would be roughly twice the cost per quality-adjusted life-year of evolocumab. This is ≈$100 000 per quality-adjusted life-year, which is a widely accepted conservative willingness-to-pay threshold by US standards. Although this analysis is based on a comparison between therapies with different levels of evidence, it is important to accept these limitations and appreciate what the value of the procedure may be in comparison with other available therapies.

PATIENT PERSPECTIVE

Challenges that may be experienced by patients undergoing LA are difficult to share objectively; they are not well documented in published studies.[103] Data regarding retention of patients treated with LA, effects on QoL, or strategies for improving long-term adherence are limited. The available studies have small sample sizes, are not stratified by specific underlying diagnoses, and are typically focused on the subpopulation of patients with HoFH, as opposed to the more common patients with HeFH, thereby limiting the generalizability of the data.[103] De Gucht et al[104] published a study conducted in Germany addressing treatment-related QoL and health-related QoL in a sample of 206 participants completing a 104-item apheresis QoL scale. Results indicated that treatment-related QoL, defined by the authors as the perceived effects of LA, might be an important determinant of health-related QoL and physical complaints in patients undergoing LA.[104] The authors suggested that further research is needed to compare QoL in patients who are receiving versus those who are not receiving LA with similar medical diagnoses, as well as that screening for effects on QoL could help support individualization of care. Wang et al[103] described factors contributing to burdens of LA therapy. Treatment challenges that may present as barriers to care included biweekly frequency, treatments affecting ability to work, cost, invasiveness, concerns about insurability, and access to treatment, given limited availability of LA facilities. With respect to patient access to treatment facilities in the United States,[98] only 33 out of 50 states have at least 1 LA treatment facility, leading to increased travel times for some patients. Unmet research needs exist for QoL studies, which include a necessity to incorporate control groups not undergoing LA, implement longer follow-up periods related to treatment retention, expand assessment of effects of social determinants of health, and conduct more detailed evaluation of long-term adherence data. Studies of QoL associated with LA treatment also need to quantify the potential for increased hospitalizations, diagnostic and interventional procedures, surgeries, cardiovascular events, disability, and death if high-risk patients are unable to be treated with LA. With respect to patient education and advocacy, the Family Heart Foundation[98] provides resources and tools, support groups, and access to lipidologists and apheresis centers.

CONCLUSIONS

With a single session, LA reduces Lp(a) and LDL-C levels by 65% to 85%; reduces inflammatory markers, prothrombotic factors, atherogenic HDL-C components, blood viscosity, and endothelial dysfunction; and improves microvascular myocardial perfusion, suggesting multiple potential mechanisms by which LA may modulate ASCVD risk. The evidence base demonstrating cardiovascular benefits of LA primarily consists of prospective and retrospective observational

data. Multiple clinical benefits have been noted with LA, which include decreased angina, increased walking distance, and plaque stabilization and regression, in addition to regression of xanthomas. Although more definitive studies are needed, the available data suggest that LA may be associated with a notable 63% to 95% reduction in incidence of MACEs. Although historically LA has been used predominantly for patients with FH with markedly elevated LDL-C levels in accordance with FDA approval in the United States, LA may have a broader range of use that may include treatment of patients without FH who have clinical ASCVD and LDL-C levels above goal despite maximally tolerated therapies or severe Lp(a) elevation. These indications are approved in several countries, but remain off-label in the United States. Use of LA for elevated Lp(a) levels (with or without elevated LDL-C levels, depending on geographically specific guidelines) may be clinically important due to the lack of effective Lp(a)-lowering therapies, but data in this population are limited. LA is also indicated under a humanitarian device exemption for treatment of primary FSGS resistant to standard treatments, possibly resulting in improved kidney function and kidney transplant preservation in about half of patients. LA is generally well tolerated and has a favorable safety profile. Although cost-effectiveness and QoL effects are important factors to consider in shared decision-making regarding treatment, LA may provide substantial clinical benefit for many high-risk patients, in whom it is frequently underused.

ARTICLE INFORMATION

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

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*Modest.

†Significant.

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Jacques Rossouw	National Heart, Lung, and Blood Institute	None	None	None	None	None	None	None
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*Modest.

†Significant.

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