INTRODUCTION

Apheresis, derived from the Greek word aphairein, meaning to take away, is applied to patients with familial hypercholesterolemia (FH) who are resistant to standard lipid level–lowering medications. Apheresis devices used for the reduction of plasma cholesterol levels can be separated into 3 general groups:

1. Nonselective plasma exchange, which simply removes all of the plasma volume through centrifugation, and was first introduced in 1967 by de Gennes and colleagues.

KEY POINTS

- Patients with familial hypercholesterolemia (FH) have early development of atherosclerosis and cardiovascular disease (CVD).
- Lipid level–lowering medications are not always successful in reducing increased low-density lipoprotein C (LDL-C) levels.
- Lipoprotein apheresis (LA) reduces LDL-C levels by more than 60% in patients with FH and reduces CVD events.
- LA also reduces lipoprotein (a) (Lp(a)) levels and CVD events.
- LA reduces inflammatory markers and blood viscosity.

KEYWORDS

- Lipoprotein apheresis
- Familial hypercholesterolemia
- LDL-C
- CVD
- Atherosclerosis
- Lp(a)

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0889-8529/16/$ – see front matter © 2016 Elsevier Inc. All rights reserved.
2. Semiselective ultrafiltration, developed by Agishi and colleagues\(^2\) in 1980, which uses a double-membrane filtration and involves elimination of atherogenic lipoproteins based on particle size and geometric properties.

3. Selective lipoprotein apheresis (LA), which was developed in 1981 by Stoffel and colleagues\(^3\) using a device containing 2 columns of sapharose gel coupled with polyclonal sheep apolipoprotein B (apoB)-100 antibodies. Newer selective LA devices have been developed involving not only antibodies to lipoproteins but negative charged environments to capture the positive charged apoB. The devices approved for use in the United States and Canada are based on the removal of charged lipoprotein particles.

CRITERIA FOR LIPOPROTEIN APERHESIS

The US Food and Drug Administration (FDA) set the criteria for LA in 1997, when the Kaneka Liposorber and B Braun HELP (heparin-induced extracorporeal low-density lipoprotein precipitation) systems were approved in the United States based on the following criteria.

Patients must show that, after 6 months of the maximum tolerated lipid level-lowering therapy and compliance with a low-saturated-fat, low-cholesterol diet, one of the following is still met:

1. Functional homozygous FH with low-density lipoprotein cholesterol (LDL-C) level greater than or equal to 500 mg/dL
2. Functional heterozygous FH with LDL-C level greater than or equal to 200 mg/dL in the presence of documented coronary artery disease (CAD)
3. Functional heterozygous FH with LDL-C level greater than or equal to 300 mg/dL in the absence of documented CAD

These requirements for therapy are much sterner than those of other countries that perform LA. In Germany, treatments are allowed for patients with CAD and LDL-C levels greater than 130 mg/dL, whereas Japan approves LA therapy for patients with CAD with a total cholesterol level greater than 250 mg/dL. To deal with this gap in treatment, some LA sites have negotiated with health care providers in allowing some high-risk patients with LDL-C levels greater than 160 mg/dL to receive LA.

Panels from the National Lipid Association (NLA) and the American Society for Apheresis (ASFA) recently recommended modifying the criterion for initiating LA therapy to include patients with any atherosclerotic cardiovascular disease (CVD), not just CAD, and lowering the LDL-C threshold in these patients to greater than or equal to 160 mg/dL.\(^4\)

POTENTIAL PATIENT POPULATION WHO QUALIFY FOR LIPOPROTEIN APERHESIS

An estimate of the LA eligible population in the United States by the strict FDA criteria, assuming a prevalence of heterozygous FH of 1 in 500, is approximately 15,000 patients eligible for LA.\(^5\) From the population of individuals intolerant of 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (statins) (prevalence 10%–25%), another 10,000 patients could be added to the number who would qualify for LA.\(^6,7\) Despite these estimates the current census in the United States of patients receiving LA is only 550. Potential explanations for the low number of patients receiving LA therapy include a lack of awareness; insufficient numbers of LA centers (fewer than 50 in the United States), resulting in patients traveling long distances for treatments; complexity of initiating an LA center; and the likelihood that patients with poor venous access will require a shunt/fistula or the belief by physicians that future lipid level-lowering drugs such as proprotein convertase subtilisin/kexin type 9 (PCSK9)
inhibitors will provide adequate treatment of these extremely high-risk patients. In contrast, to achieve a successful LA program requires a team effort by the patients, medical staff, and health care providers.

BILLING AND CODING INFORMATION

LA therapy is covered by most private health insurers and government payers (eg, Medicare, Department of Veterans’ Affairs). Coverage policies are typically based on the FDA indications but exceptions have been allowed (ongoing CVD and increased Lp(a) or LDL-C level more than 160 mg/dL). These exceptions are made on a case-by-case basis and may also depend on the health care provider and the state residency of the patient. Reimbursement for LA in the hospital or outpatient setting can be highly variable ($2000–$4000 per session) according to the insurer and the location in the United States.

In 2005, relative value units (RVUs) were specified for current procedural terminology (CPT) 36516. This specification applies exclusively to LA. In 2005 and 2006, about 85 RVUs were designated for this procedure and associated services under the direct supervision of physicians. Under the applicable ambulatory payment classification (APC 0112), Medicare payments are usually less than reimbursement under contracts negotiated between hospital providers and private insurers. It is recommended that all cases separately bill the insurer for professional services and again under CPT 36516.

APPROVED LIPOPROTEIN APHERESIS MACHINES IN THE UNITED STATES

Futura, B Braun, Melsungen, Germany

**Heparin-induced extracorporeal low-density lipoprotein precipitation**

In 1983, Wieland and Seidel\(^8\) introduced the HELP system (Fig. 1). Following separation, the plasma is mixed 1:1 with a 0.3-M acetate buffer (pH 4.8) solution containing heparin at a concentration of 100 U/mL. Precipitation of heparin and low-density lipoprotein (LDL) occurs when the plasma buffer solution reaches an approximate pH of 5.2. The mechanism for the selective removal of lipoproteins is attributed to the negatively charged heparin precipitating with the positively charged apoB of LDL-C.

![HELP (Futura)](image)

*Fig. 1. HELP (Futura). (From Moriarty PM. Low-density lipoprotein apheresis. In: Ballantyne CM, editor. Clinical lipidology: a companion to Braunwald’s heart disease. Philadelphia: Saunders Elsevier; 2009. p. 365; with permission.)*
very-low-density lipoproteins (VLDLs), and Lp(a). High-density lipoprotein cholesterol (HDL-C), which has a negatively charged membrane,9 is normally spared from the precipitation process. A diethylaminoethyl cellulose filter adsorbs the residual heparin in the LDL-free plasma. Physiologic pH of the plasma and removal of excess fluid are achieved by dialysis and ultrafiltration.10

**MAO3 Liposorber, Kaneka, Osaka, Japan**

**Dextran sulfate low-density lipoprotein adsorption**

In 1987, Mabuchi and colleagues11 reported on the dextran sulfate LDL adsorption (DSA) system (LA-15, Kaneka, Osaka, Japan) (Fig. 2). Plasma is exposed to a column of cellulose beads coated with dextran sulfate cellulose. Similar to the HELP system, selective removal of LDL, VLDL, and Lp(a) occurs through an electrostatic interaction of the polyanionic dextran sulfate ligands and the positively charged apoB lipoproteins. The machine contains 2 dextran sulfate columns. After the first column is exposed to 500 mL of plasma, it is then cleansed and regenerated with a solution containing 4.1% sodium chloride. During the first column’s rinsing process, plasma flow is redirected to the second column. As with the HELP system, the DSA system retains most of the HDL in the plasma.

**Further lipoprotein apheresis information**

A heparin bolus (2000–4000 IU) is used to achieve anticoagulation, followed by a continuous infusion of heparin at 1500 IU/h. Both treatments are performed through a peripheral antecubital venous access (needles of 16–18 gauge) or an arteriovenous fistula. At flow rates between 40 and 100 mL/min, treated plasma volume varies between the two machines. The HELP system treats 3000 mL of plasma and additional volume would overtax the collecting capability of its precipitating filter or increase

![Fig. 2. DSA (MAO3). (From Moriarty PM. Low-density lipoprotein apheresis. In: Ballantyne CM, editor. Clinical lipidology: a companion to Braunwald’s heart disease. Philadelphia: Saunders Elsevier; 2009. p. 366; with permission.)](image-url)
bleeding risk because of lower fibrinogen levels. For the DSA system, each of the 2
dextran sulfate filters are cleansed after exposure to 500 mL of plasma, allowing an
unlimited amount of plasma volume treated as long as its plasma separator remains
patent. Plasma volume treated with the DSA system is based on the patient’s body
mass and hematocrit. During therapy, only a maximum of 300 to 600 mL of plasma/
blood are extracorporeal at any time. Treatments last 2 to 4 hours (1.5–3 hours patient
time and 1 hour nursing time for before and after the session) and are scheduled
weekly, biweekly, or even less frequently, depending on baseline lipid levels and
response to therapy. The biweekly treatments are most common.

**Contraindications/Complications/Adverse Events**

The HELP and DSA systems are contraindicated for patients with hypersensitivity to
heparin. In cases of sensitivity to heparin, the broad-spectrum synthetic protease inhu-
bitor nafamostat mesilate has sometimes been used with the DSA system as an
alternative anticoagulant. The occurrence of adverse events (AEs) is low and typically
involves the blood circulating outside the body. Hypotension is the most common
AE (<2%) and the incidence of all other AEs (flushing, blotching, chest pain, anemia,
abdominal discomfort, hemolysis, and arrhythmia) is less than 1%. Unlike
HELP, the DSA system increases plasma bradykinin (BK) levels by 900-fold. BK is a
potent vasodilator and increase of plasma levels may cause an anaphylactoidlike re-
action for patients also receiving angiotensin-converting enzyme inhibitors (ACEIs),
which are blockers of BK degradation. To prevent this reaction, patients should dis-
continue the use of ACEI or switch to an angiotensin receptor blocker.

**Special Points of Interest**

The DSA system is recommended for children with FH if they weigh more than 15 kg (33
lb) and are older than 5 years of age, whereas with the HELP system it is suggested that a
patient’s weight should be more than 37 kg (80 lb) before initiating therapy. Although not
recommended, case studies have shown LA safety and effectiveness for women with FH
throughout their pregnancies. Plasma fibrinogen, a multifaceted protein involved in the
vascular process of inflammation, coagulation, and viscosity, is acutely lowered by 65%
with the HELP system compared with 30% or less with the DSA system.

**Clinical Benefit**

Because of the small number of patients receiving LA therapy and the unethical prac-
tice of sham therapy, there is a lack of large, multicenter, placebo-controlled trials.
One of the largest nonrandomized trials followed the safety and efficacy of LA therapy
(DSA) over a 6-year period. The study compared FH heterozygotes (n = 43) with CVD
receiving LA plus combination lipid level-lowering therapy (low-dose statin plus pro-
bucol and resin or fibrate) with a similar group of FH heterozygotes (n = 87) receiving
only lipid level-lowering therapy. Kaplan-Meier analysis of the primary end points
(nonfatal myocardial infarction, coronary angioplasty, coronary artery bypass, and
death from coronary heart disease [CHD]) found that the rate of events was 72% lower
in the LA group (10%) compared with the drug-only group (36%) (P = .008). Fig. 3
shows the relative risk reduction found in multiple studies.

**LIPOPROTEINS AND OTHER PROTEINS ALTERED BY LIPOPROTEIN APHERESIS**

**Low-density Lipoprotein (Apolipoprotein B–containing Particles)**

LA acutely reduces apoB-containing particles by approximately 60% (see Table 1).
Typically, the greater the baseline LDL-C level, the greater the reduction of apoB lipo-
proteins. The rebound of LDL-C and Lp(a) to approximately baseline levels ranges
from 8 to 13 days. Using multiple therapies along with LA, such as statins, increases the efficacy of LA and increases the probability of treatment success, even in patients homozygous for FH. Further, after chronic LA therapy, the pretreatment levels of apoB lipoproteins, such as LDL-C, are reduced by 20% to 40%.

Along with the reduction of apoB lipoproteins, LA also modifies the composition of plasma LDL. Increased circulating levels of oxidized LDL (ox-LDL) and small dense LDL have been associated with an increased risk of CVD. LA significantly reduces ox-LDL levels and decreases small dense LDL levels, whereas the total percentage of large buoyant LDL increases after treatment. Despite the quantitative and qualitative changes to LDL, regular apheresis therapy does not seem to alter kinetic parameters of apoB metabolism.

**High-density Lipoprotein Cholesterol**

HDL-C levels are reduced and its functionality (reverse cholesterol transport activity) may be impaired in patients with FH. The mechanism by which LA acutely lowers HDL-C (10%–20%) is not fully understood because, unlike apoB lipoproteins, the HDL-C is negative charged. Some explanations involve filtration, hemodilution, activation of hepatic triglyceride lipase (HTGL), or the decreased activity of lecithin-cholesterol acyltransferase. Several studies of LA therapy have revealed a greater acute reduction of total HDL than apolipoprotein A-I, the primary HDL lipoprotein involved in reverse cholesterol transport, and that most of the HDL-C removed following LA is a proinflammatory type, as measured by the inability of HDL to inhibit LDL-induced monocyte chemotactic activity.

Apolipoprotein E4 (ApoE4), a risk factor for CVD and Alzheimer disease, is a component of HDL-C that increases its binding affinity to the LDL receptor more than LDL-C. Patients with FH seem to have a greater amount of ApoE4-bound HDL-C and LA therapy acutely removes this protein complex by more than 40%. Acutely, total HDL-C returns to pretreatment levels in 24 hours, whereas long-term therapy preserves or enhances baseline levels. LA significantly reduces LDL/HDL ratios and reduces more HDL (2.5 times) than apolipoprotein A1 (ApoA1), whereas nonselective plasma exchange increases LDL/HDL ratios and reduces equal amounts of HDL and ApoA1. This difference is one of the significant distinctions between nonselective and selective apheresis.

HDL particle (HDL-P) number has been shown to be inversely associated with CHD, independent of total HDL-C levels and/or other atherogenic lipoproteins. LA therapy acutely increases HDL-P by 16% and reduces total HDL-C levels.
Triglycerides and Other Apolipoproteins

Triglycerides (TGs) are acutely reduced by 18% to 64% (Table 1) following LA. Similar to HDL-C, TG levels rebound to near pretreatment levels in 24 hours. Reduction in TG levels have been attributed to the removal of the apoB portion of VLDL, HTGL activation, and heparin’s ability to increase lipoprotein lipase activity. LA therapy also reduces apolipoprotein C-III and apoE levels by 40% to 50%.

Lp(a)

The treatment of increased Lp(a) levels is not an FDA-approved indication in the absence of meeting the LDL-C criterion. However, the latest data reveal an increased atherogenicity and risk of CVD associated with Lp(a) regardless of LDL-C levels. In 2010 the German government approved LA treatments for patients with ongoing CAD and Lp(a) levels greater than 60 mg/dL (Normal<30 mg/dL), irrespective of LDL-C levels. Since initiating LA for increased Lp(a) levels, 3 retrospective/prospective trials have discovered a 70% to 81% reduction of major adverse cardiovascular events (Table 2). In the United States a few patients with isolated increased Lp(a) levels and ongoing CVD are receiving biweekly LA therapy.

Inflammatory and Other Markers Affected

In addition to lipoproteins, LA modifies other markers associated with vascular disease, in particularly inflammatory proteins. Table 3 lists immediate changes to certain plasma proteins following LA.

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**Table 1**

<table>
<thead>
<tr>
<th>Lipid</th>
<th>HELP (%)</th>
<th>DSA (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol</td>
<td>42–54</td>
<td>48–68</td>
</tr>
<tr>
<td>LDL-C</td>
<td>55–61</td>
<td>49–85</td>
</tr>
<tr>
<td>HDL-C</td>
<td>0–19</td>
<td>4–32</td>
</tr>
<tr>
<td>Lp(a)</td>
<td>55–68</td>
<td>19–70</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>20–61</td>
<td>26–64</td>
</tr>
</tbody>
</table>


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**Table 2**

<table>
<thead>
<tr>
<th>Apheresis</th>
<th>Jaeger et al., 2009</th>
<th>Rosada et al., 2014</th>
<th>Leebmann et al., 2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n)</td>
<td>Before</td>
<td>After</td>
<td>Before</td>
</tr>
<tr>
<td></td>
<td>120</td>
<td>120</td>
<td>37</td>
</tr>
<tr>
<td>Duration (y)</td>
<td>5.5</td>
<td>5.0</td>
<td>5.2</td>
</tr>
<tr>
<td>LDL-C (mg/dL)</td>
<td>125</td>
<td>45 (−65%)</td>
<td>84</td>
</tr>
<tr>
<td>Lp(a) (mg/dL)</td>
<td>118</td>
<td>33 (−72%)</td>
<td>112</td>
</tr>
<tr>
<td>MACE total</td>
<td>297</td>
<td>57 (−81%)</td>
<td>67</td>
</tr>
<tr>
<td>MACE per year</td>
<td>1.05</td>
<td>0.14 (−86%)</td>
<td>2.80</td>
</tr>
</tbody>
</table>

Percentages are mean percent change.

*Abbreviation: MACE, major adverse cardiac events.*
Table 3
Acute changes to vascular markers following LA

<table>
<thead>
<tr>
<th>Marker</th>
<th>Acute Changes (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Proinflammatory</strong></td>
<td></td>
</tr>
<tr>
<td>MCP-1</td>
<td>−15 to −18</td>
</tr>
<tr>
<td>MMP-9</td>
<td>−20</td>
</tr>
<tr>
<td>TIMP-1</td>
<td>−30</td>
</tr>
<tr>
<td>LBP</td>
<td>−27</td>
</tr>
<tr>
<td>Lp-PLA2</td>
<td>−22</td>
</tr>
<tr>
<td>VEGF</td>
<td></td>
</tr>
<tr>
<td>VEGF</td>
<td>25 to 45</td>
</tr>
<tr>
<td>IGF-I</td>
<td>−37</td>
</tr>
<tr>
<td>Brdykinin</td>
<td>0&gt;2000</td>
</tr>
<tr>
<td>ET-1</td>
<td>−15 to −75</td>
</tr>
<tr>
<td>PGI2</td>
<td>300</td>
</tr>
<tr>
<td><strong>Vascular Function</strong></td>
<td></td>
</tr>
<tr>
<td>Nitric oxide</td>
<td></td>
</tr>
<tr>
<td>Nitric oxide</td>
<td>25 to 45</td>
</tr>
<tr>
<td><strong>Thrombotic</strong></td>
<td></td>
</tr>
<tr>
<td>Tissue factor</td>
<td>−26</td>
</tr>
<tr>
<td>Von Willebrand factor</td>
<td>−29 to −56</td>
</tr>
<tr>
<td>Thrombin</td>
<td>−55</td>
</tr>
<tr>
<td>Factor V</td>
<td>−57 to −74</td>
</tr>
<tr>
<td>Factor VII</td>
<td>−4 to −36</td>
</tr>
<tr>
<td>Factor XI</td>
<td>−27 to 82</td>
</tr>
<tr>
<td>Factor XII</td>
<td>−32 to 73</td>
</tr>
<tr>
<td>sCD40L</td>
<td>−16</td>
</tr>
<tr>
<td>Homocysteine</td>
<td>−15 to −25</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>−10 to −65</td>
</tr>
<tr>
<td><strong>Fibrinolytic</strong></td>
<td></td>
</tr>
<tr>
<td>Plasminogen</td>
<td>−23 to −50</td>
</tr>
<tr>
<td>Protein S</td>
<td>−11 to −35</td>
</tr>
<tr>
<td>Protein C</td>
<td>−32 to −48</td>
</tr>
<tr>
<td>Antithrombin</td>
<td>−11 to −25</td>
</tr>
</tbody>
</table>

High variation of values may be partially caused by differences in treated plasma and blood volumes.

**Abbreviations:** CRP, C-reactive protein; ET-1, endothelin-1; ICAM-1, intercellular adhesion molecule-1; IGF-I, insulin-like growth factor-I; LBP, lipopolysaccharide binding protein; Lp-PLA2, lipoprotein-associated phospholipase A2; MCP-1, monocyte chemotactant protein-1; MMP-9, matrix metalloproteinase-9; PGI2, prostaglandin I2; SAA, serum amyloid A; sCD40L, soluble CD40 ligand; TIMP-1, tissue inhibitor of metalloproteinase-1; VEGF, vascular endothelial growth factor.

Vascular cells in response to injury secrete pentraxin 3, a member of the humoral arm of innate immunity. Pentraxin 3 levels are also increased in patients with FH and its level is strongly associated with vascular disease. Zanetti and colleagues found that LA therapy acutely and chronically reduced plasma levels of pentraxin 3. The reduction of these inflammatory and lipoproteins seems to markedly reduce plaque inflammation, as shown by van Wijk and colleagues when they used F-fluorodeoxyglucose PET before and after LA (Fig. 4).

RHEOLOGY

Hemorheology, or blood rheology, is the study of flow properties of blood and its elements. Blood viscosity is a measure of the resistance of blood to flow. Unlike plasma, blood behaves as a non-newtonian fluid, such that its viscosity varies with shear forces (rate or stress). The variation in viscosity is directly related to vascular resistance, which can profoundly influence CVD and atherosclerosis. Mediators of blood viscosity (in addition to hematocrit, shear forces, and temperature) include red blood

<table>
<thead>
<tr>
<th>Markers</th>
<th>HELP</th>
<th>Liposorber</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma viscosity</td>
<td>−15</td>
<td>−11</td>
</tr>
<tr>
<td>Blood viscosity</td>
<td>−15</td>
<td>−5</td>
</tr>
<tr>
<td>RBC aggregation</td>
<td>−52</td>
<td>−31</td>
</tr>
<tr>
<td>RBC deformability</td>
<td>45</td>
<td>45</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>−62</td>
<td>−11</td>
</tr>
</tbody>
</table>

Comparison from head-to-head study between HELP and Liposorber.

*P less than .05.

Data from Refs. 70–74
cell (RBC) deformability, RBC aggregation, and plasma viscosity. A single LA treatment reduces blood viscosity by more than 20% and maintains this reduction for at least 7 days. The improvement of blood rheology by LA is related to changes in RBC aggregation/deformability and plasma viscosity. Fibrinogen is responsible for 20% of plasma viscosity, which explains why the Futura HELP system LA improves rheology factors more effectively than the Liposorber DSA system (Table 4).

ALTERNATIVE USES

When standard therapy has failed, LA can be used for complex vascular diseases in which pathologic components of the blood or plasma need to be removed (Box 1). As mentioned previously, LA is performed in Germany for patients with increased plasma levels of Lp(a) and ongoing CVD, whereas clinicians in Japan treat more patients who have advanced (Fontaine classification II) peripheral arterial disease than patients with FH. In 2013 the FDA approved LA therapy (DSA) for pediatric patients with primary focal segmental glomerulosclerosis (FSG) either before or after renal transplant. These alternative uses, and others, are listed in Box 1. Besides FSG, the FDA has approved none.

SUMMARY

LA therapy has proved its clinical benefit in reducing CVD events for patients with FH with hypercholesterolemia. Present FDA guidelines for the use of LA are based on 25-year-old data and more recent studies have shown that lower levels of plasma cholesterol, even in combination with a statin, further reduce CVD risk. Although lacking in multicenter randomized control studies, for the past 40 years LA therapy has extended the lives of the FH population, in particular homozygote patients.

The reduction of Lp(a) levels, improved rheology, and improved quality of HDL-C may be independent mechanisms by which LA reduces CVD. It seems that the removal of plasma inflammatory markers along with atherogenic lipoproteins might play a role in the immediate reduction of arterial wall inflammation. These potential benefits of LA would be further appreciated and implemented as therapy if more randomized clinical trials were performed using this technology in patients with other categories of vascular disease not necessarily associated with FH.

Despite the success of reducing LDL-C levels and almost universal coverage, only 2% of potential candidates are presently receiving LA therapy in the United States. Recently, the NLA, ASFA, and FH Foundation publically voiced their support for LA
therapy and the need for patients to be offered this technology if they qualify. The future for most patients with FH may be aligned with newer lipid level–lowering medications such as PCSK9 inhibitors, but until that time LA is the most effective treatment available for this high-risk patient population.

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REFERENCES


