

Review Article

Toward an international consensus—Integrating lipoprotein apheresis and new lipid-lowering drugs

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BACKGROUND: Despite advances in pharmacotherapy of lipid disorders, many dyslipidemic patients do not attain sufficient lipid lowering to mitigate risk of atherosclerotic cardiovascular disease. Several classes of novel lipid-lowering agents are being evaluated to reduce atherosclerotic cardiovascular disease risk. Lipoprotein apheresis (LA) is effective in acutely lowering the plasma concentrations of atherogenic lipoproteins including low-density lipoprotein cholesterol and lipoprotein(a), and novel lipid-lowering drugs may dampen the lipid rebound effect of LA, with the possibility that LA frequency may be decreased, in some cases even be discontinued.

SOURCES OF MATERIAL: This document builds on current American Society for Apheresis guidelines and, for the first time, makes recommendations from summarized data of the emerging lipid-lowering drug classes (inhibitors of proprotein convertase subtilisin/kexin type 9 or microsomal triglyceride transfer protein, high-density lipoprotein mimetic), including the available evidence on combination therapy with LA with respect to the management of patients with dyslipidemia.

ABSTRACT OF FINDINGS: Recommendations for different indications are given based on the latest evidence. However, except for lomitapide in homozygous familial hypercholesterolemia and alirocumab/evolocumab in heterozygous familial hypercholesterolemia subjects, limited data are available on the effectiveness and safety of combination therapy. More studies on combining LA with novel lipid-lowering drugs are needed.

CONCLUSION: Novel lipid-lowering agents have potential to improve the performance of LA, but more evidence is needed. The Multidisciplinary International Group for Hemapheresis Therapy and Metabolic Disturbances Contrast scientific society aims to establish an international registry of clinical experience on LA combination therapy to expand the evidence on this treatment in individuals at high cardiovascular disease risk.

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Executive summary of recommendations

Clinical practice recommendations are made based on standard grades of evidence (Box 1), and are based on guidance from the American Society for Apheresis (ASFA; Appendix 1).¹ A treatment algorithm is provided in Figure 1.

Using the ASFA guidelines as a starting point,¹ we considered what clinical research has been done to improve lipoprotein apheresis (LA) since the publication of the ASFA document. We particularly focused on the novel pharmacotherapies that may be used in conjunction with LA. Importantly, given the relatively small number of publications in this field, we did not conduct a structured literature search and instead gathered all available evidence in article and abstract form and applied evidence grades thereon (Box 1).² Grades were applied according to 80% consensus among the author panel.

1. Homozygous familial hypercholesterolemia
 - ASFA category I (disorder for which apheresis is accepted as first-line therapy, either as a primary stand-alone treatment or in conjunction with other modes of treatment; Appendix Table A1)
 - 1.1. In addition to diet, statins, ezetimibe, and other lipid-lowering therapies, LA can be effective in reducing low-density lipoprotein cholesterol

(LDL-C) levels and cardiovascular disease (CVD) events, and prolonging life. (1A)

- 1.2. Novel lipid-lowering therapies are indicated in patients not attaining sufficient lipid lowering. The European Atherosclerosis Society Consensus panel recommends LDL-C <2.5 mmol/L (<100 mg/dL) or <1.8 mmol/L (<70 mg/dL) in adults with clinical atherosclerotic cardiovascular disease (ASCVD). For children, <3.5 mmol/L (<135 mg/dL) is recommended.³ (2A)
- 1.3. Residual low-density lipoprotein receptor (LDLR) activity should be determined. Measuring this is relatively complicated and requires specific facilities, but a genetic diagnosis is sufficiently informative in most cases.
 - 1.3.1. If a patient is compound or double heterozygote, some LDLR activity is likely to remain; therefore, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are probably effective. (2B)
 - 1.3.2. If a patient has 2 null mutations, and therefore no remaining LDLR activity, or has autosomal recessive hypercholesterolemia, PCSK9 inhibitors cannot reduce LDL-C. In these patients, lomitapide is a better treatment option. Mipomersen can be used in the United States, but not in Europe. (2B)

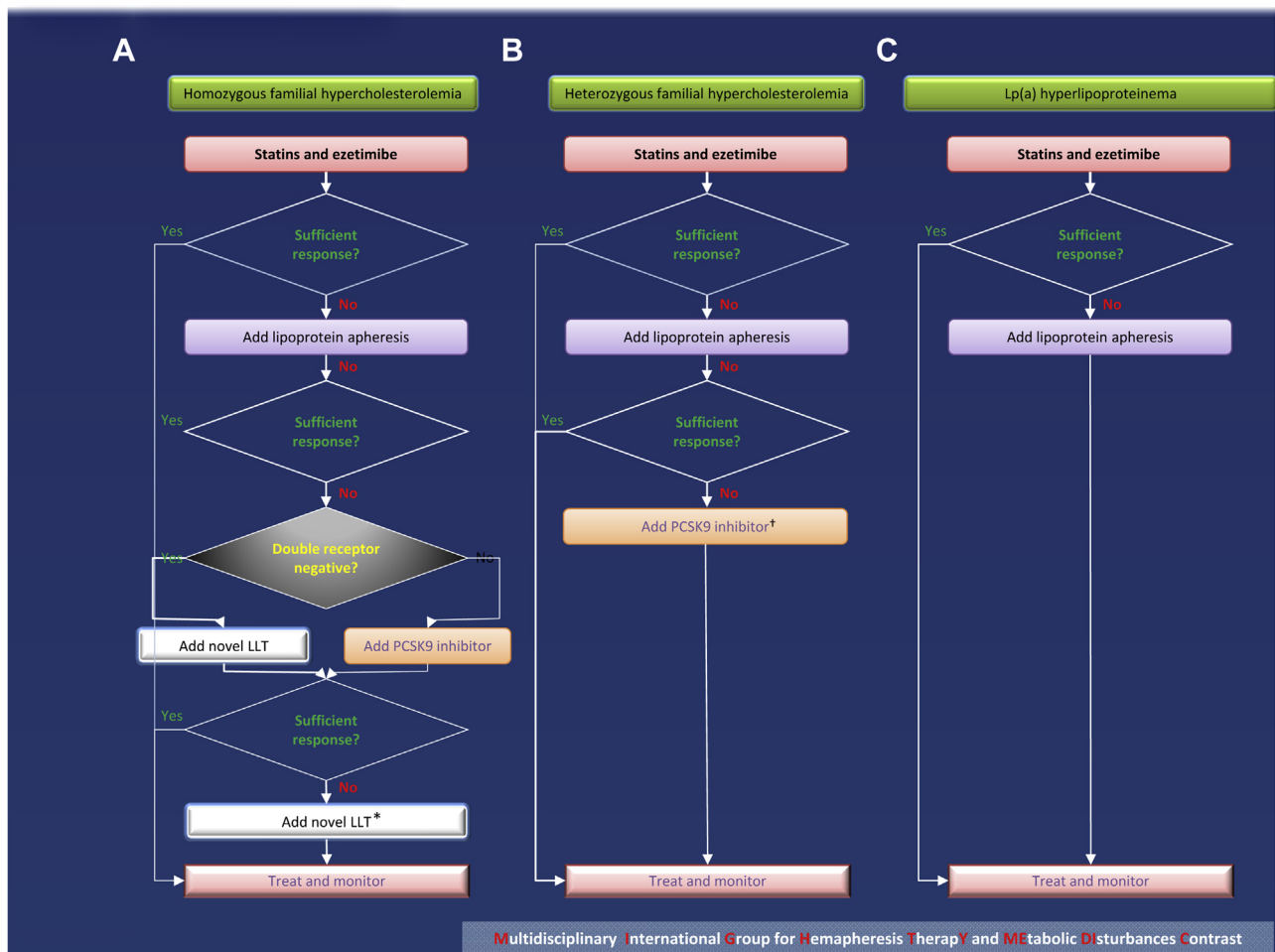


Figure 1 Treatment algorithm for (A) HoFH, (B) HeFH and (C) Lp(a) hyperlipoproteinemia. *PCSK9 inhibitors are likely to work in HoFH only if the patient has defective, rather null LDL receptors on both alleles; †in HeFH, the order in which PCSK9 inhibitors and LA might be tried is a topic of current debate, and some physicians may prefer to try PCSK9 inhibitor before LA—there are no other options for HeFH therapy in patients who fail to respond to statins and ezetimibe. HeFH, heterozygous familial hypercholesterolemia; HoFH, homozygous familial hypercholesterolemia; Lp(a), lipoprotein (a); LLT, lipid-lowering therapy; PCSK9, proprotein convertase subtilisin/kexin type 9; example real-world treatment protocols for HoFH are documented in Stefanutti C, et al. *J Clin Lipidol* 2016; 10:782-9.⁴ “Sufficient response” refers to a clinical effect that meets the requirements set out in relevant, disease-specific guidance.

Box 1. Levels of evidence and grades of recommendation.

Levels of evidence

- 1 systematic review/meta-analysis/at least 1 randomized controlled trial/good quality diagnostic tests.
- 2 good quality clinical or observational studies.
- 3 expert opinion or clinical experience/argument from first principles.

Grades of recommendation

- A can be trusted to guide practice.
 B can be trusted to guide practice in most situations.
 C can be used to guide practice, but care should be taken in application.

Evidence grading methodologies are given in [Appendix Tables A1–A2](#).

2. Heterozygous familial hypercholesterolemia ASFA category II (disorder for which apheresis is accepted as second-line therapy, either as a stand-alone treatment or in conjunction with other modes of treatment; [Appendix Table A1](#))
 - 2.1. In addition to diet, statins, ezetimibe, and other lipid-lowering therapies, LA can be effective to reduce LDL (and therefore LDL-C) levels and CVD events. (1A)
 - 2.2. Novel lipid-lowering therapies such as PCSK9 inhibitors are indicated in patients not achieving sufficient lipid lowering. PCSK9 inhibitors are monoclonal antibodies and may be adsorbed by LA; therefore, administration of a PCSK9 inhibitor should be done after the LA procedure. We accept that some physician may prefer to try PCSK9 inhibitors before LA, but at the time of writing, the body

of evidence for the efficacy of LA on ASCVD endpoints is greater than that for PCSK9 inhibitors. (1A)

- 2.3. Preliminary data on combination therapy of LA and novel lipid-lowering therapies in HeFH suggest that it may lower LA frequency in some patients. Some patients may even stop LA. (3C)

Summaries of ASFA 2016 recommendations for homozygous familial hypercholesterolemia and HeFH are given in [Appendix Table A3](#).

3. Lp(a) hyperlipoproteinemia

ASFA category II (disorder for which apheresis is accepted as second-line therapy, either as a stand-alone treatment or in conjunction with other modes of treatment; [Appendix Table A1](#)).

- 3.1. Lp(a) mass should be measured once in all subjects at intermediate or high risk of CVD/CHD who present with premature CVD, FH, a family history of premature CVD without elevated LDL-C levels or recurrent CVD despite statin treatment. (1A)
- 3.2. Lp(a) mass <30 mg/dL (<45 nmol/L) is considered normal. (Normal lab value; 1A)
- 3.3. Nicotinic acid (1–3 g/d) used to be first-line treatment, but is no longer available in Europe.
- 3.4. If refractory, weekly selective LA is effective to reduce Lp(a) mass when administered on long-term basis. (3C)

The most important concept underlying treatment of monogenic or multigenic hyperlipidemias is that established asymptomatic, symptomatic, recurrent, or progressive ASCVD must be tackled with intensive treatment by means of all available lipid-lowering therapies.

The ASFA 2016 guidelines, which we used as a basis to build drug-specific recommendations, do not include recommendations for imaging, pregnancy, or application of multidisciplinary care, and these topics remain out of scope for the present review.

Introduction

Lipoprotein apheresis (LA) refers to extracorporeal selective elimination of apolipoprotein B (apoB)100-containing lipoproteins. Its primary goal is lowering plasma concentrations of atherogenic lipoproteins in patients with severe hyperlipidemia or hyperlipoproteinemia in whom lipid levels are not adequately controlled with diet and pharmacotherapy. LA is the cornerstone of lipid lowering in homozygous familial hypercholesterolemia (HoFH) and severe heterozygous familial hypercholesterolemia (HeFH) when traditional lipid-lowering drugs are not sufficiently effective.⁵ Guidance for the use of apheresis has been issued across indications by American Society for Apheresis (ASFA),¹ and for familial hypercholesterolemia (FH) by the International FH

foundation.² The European Atherosclerosis Society (EAS) issues general guidance for the treatment of HoFH,³ and HEART UK has also issued guidance on HoFH, which includes use of LA.⁶ In addition, a recent consensus panel has developed guidance for phenotypic diagnosis of HoFH.⁷

By means of adsorption, precipitation, or filtration, LDL particles including low-density lipoprotein cholesterol (LDL-C) and lipoprotein(a) (Lp(a)) are removed from the plasma or whole blood.

Indications for LA

Homozygous familial hypercholesterolemia

HoFH is characterized by high serum cholesterol and LDL-C levels, appearance of xanthomas in the first decade of life and (signs of) hypercholesterolemia in both parents. HoFH patients often present with a family history of premature coronary artery disease (CAD). They may show signs of cholesterol deposits in eyes and tendons (arcus cornealis and xanthomas).^{7,8}

HoFH can be the result of homozygosity/compound/double heterozygosity for mutations in the genes encoding LDLR (*LDLR*: OMIM #606945), apolipoprotein B (*APOB*: OMIM #107730), proprotein convertase subtilisin/kexin type 9 (*PCSK9*: OMIM #607786) or the LDLR adaptor protein 1 (*LDLRAP1* or *ARH* for autosomal recessive hypercholesterolemia, OMIM# 605747).⁹ These different molecular entities all interfere with the LDL–LDLR metabolism, yielding extremely high LDL-C levels. Null or receptor deficient and defective mutations occur. Residual LDLR activity determines the severity of the phenotype of HoFH and likely affects response to treatment if the mechanism of action of a drug requires residual LDLR function. Carriers of these genetic aberrations are exposed to extremely elevated LDL-C levels from birth onward. Case reports have described extensive atherosclerotic vascular disease and development of aortic stenosis in relation to HoFH, starting in early childhood.^{3,10} Early detection and intervention are important to attenuate atherogenesis and improve life expectancy.

Heterozygous familial hypercholesterolemia

Phenotypic variability is large among HeFH individuals and LDL-C levels have been reported to largely overlap with HoFH, as well as with individuals without HeFH.¹¹ Most HeFH patients remain undiagnosed, which is a problem since their LDL-C levels can be elevated from birth and may reach 7.5 to 12 mmol/L (290–464 mg/dL).¹²

Lp(a) hyperlipoproteinemia

Lp(a) is a unique lipoprotein consisting of an LDL particle covalently bound by disulphide bridges to a highly glycosylated protein called apolipoprotein(a) (apo(a)), which is under

tight genetic regulation. Lp(a) is accordingly a quantitative genetic trait that has atherothrombogenic, proinflammatory, and pro-oxidative properties. Its plasma concentration is chiefly determined by the rate of hepatic secretion of apo(a) that in turn is inversely related to the size of apo(a) and hence the copy number of genetic variants that encode the number of K-IV2 repeats of the apo(a) protein.^{13–17} Under physiological conditions, levels of Lp(a) mass are typically higher during pregnancy, after menopause, and in patients with diabetes and end-stage renal disease. Lp(a) is involved in various processes related to atherosclerosis and vascular disease, with an overall proatherogenic effect that is similar to LDL-C, as well as having a prothrombotic effect.

An essential aspect of the Lp(a) molecule is the tail of the apo(a) moiety containing Kringle proteins IV and V. Kringle IV consists of 10 subtypes or segments (numbered 1–10), of which subtype 2 has an individually variable number of copies (3–40). Hepatic production and secretion of smaller, low molecular weight (MW) apoprotein (a), which contain low Kringle IV-2 copy numbers is more rapidly produced and secreted than larger, high MW apoprotein (a), which have higher IV-2 copy numbers. Paradoxically patients with the more easily produced and secreted smaller, low MW isoforms have higher Lp(a) mass concentrations and those with the high MW isoforms. The length of Kringle IV-type 2 repeats is genetically determined and not influenced by lifestyle.¹⁸ Levels of Lp(a) mass may vary up to a 1000-fold between individuals.

Lp(a) was identified as an independent CHD risk factor in men of the Framingham Offspring Cohort (relative risk: 1.9, 95% confidence interval: 1.2–2.9), and other studies have added evidence supporting the association.¹⁹ Data of genetic studies are consistent with a causal association between elevated Lp(a) mass levels and increased risk of myocardial infarction and CAD.¹⁸

The EAS has established the 80th percentile Lp(a) mass concentration as a target level (corresponding to below 50 mg/dL) for both primary and secondary prevention.²⁰ The ACC/AHA guidelines do not specify an Lp(a) treatment goal.²¹ However, the National Lipid Association reports Lp(a) mass >50 mg/dL (protein; isoform insensitive assay) as a high-risk biomarker.²²

Clinical effects of LA

LA is a safe and generally well-tolerated procedure to lower LDL and Lp(a) and is thought to result in reasonably good quality of life (QoL),²³ although recent data suggest that the negative impact of LA on QoL is similar to that of hemodialysis.²⁴ Owing to its invasive nature and ethical concerns, no randomized clinical trials have been performed to evaluate its efficacy. However, abundant clinical experience shows that if applied once weekly, close to acceptable LDL-C levels can be achieved.²⁵

Long-term, continuous treatment with LA can mobilize a significant amount of cholesteryl esters from intracellular

storage, and weekly or biweekly LA has been shown to result in regression of xanthomas and xanthelasmata in young individuals with severe genetic hypercholesterolemia.²⁶ Clinical evidence also suggests that long-term LA contributes to plaque regression and/or stabilization, as well as improvements in prognosis.^{26,27}

In HoFH, profound lowering of LDL by LA appears to improve coronary atherosclerosis and aortic valvular disease and increase longevity, particularly when treatment is initiated at an early age.²⁸ Initiation of LA in very young, physically light children can be problematic, but is routinely achieved by skilled medical teams.

Regarding QoL, the considerations for LA are complex. Although LA has the potential to prolong life,²⁹ it brings with it the additional burden of treatment schedules. A case series of 24 patients with HoFH found that the overall burden of disease was high, but the study was not designed to separate disease burden from treatment burden and was not powered to detect differences in QoL parameters between treatment modalities.³⁰

Pleiotropic effects of LA

In addition to lowering lipid levels, LA exerts pleiotropic effects. In response to various apheresis techniques, levels of both pro-inflammatory and anti-inflammatory factors may change. It is hitherto unclear whether the effect of LA on circulating inflammatory markers is related to the direct removal of inflammatory substances or to altered cytokine expression (Fig. 2).³¹

Activation of complement in response to LA has been described, as well as reduction of high-sensitivity C-reactive protein, a marker of inflammation. Other anti-inflammatory effects include a reduction of oxidized LDL, P-selectin, and intercellular adhesion molecule1.^{34,35} Moreover, a significant reduction of arterial inflammation has been observed after LA in patients with FH.^{33,36}

Furthermore, induction of vasodilation and improved blood flow through stimulation of expression of endothelium-derived nitric oxide is seen, and changes in factors affecting vascular permeability. Vascular resistance due to improved blood rheology, a major determinant for microvascular perfusion, is significantly reduced after LA therapy. Blood/plasma viscosity and red blood cell aggregation/deformability are improved with LA.³⁷ Significant downregulation of messenger RNA encoding the endothelial damage marker pentraxin-3 was seen after the first LA session, while soluble plasma pentraxin-3 levels did not change, but high-sensitivity C-reactive protein levels did.³⁸

Recently, it was demonstrated that LA therapy also removes PCSK9 in patients with severe FH.^{35,39} This was confirmed in a study of 40 patients, and the effect was found to extend to a range of LA types.³⁵ Both mature and furin-cleaved forms of PCSK9 are removed by LA.⁴⁰ Lower PCSK9 levels are associated with lower LDL-C levels.

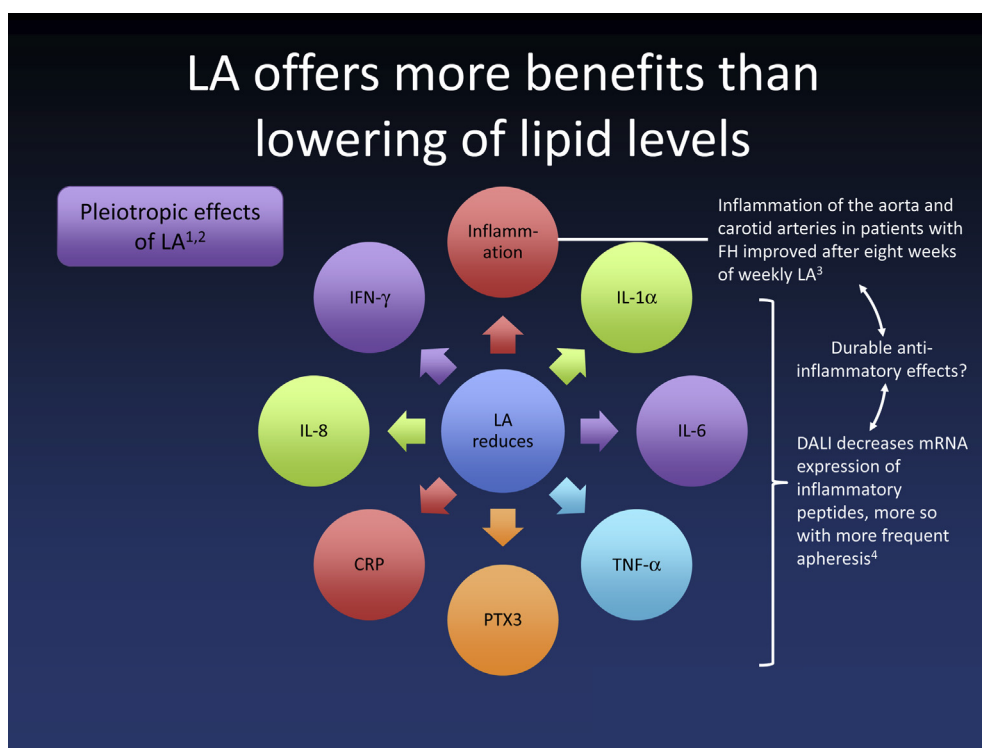


Figure 2 Lipoprotein apheresis offers more benefits than lowering of lipid levels. Pleiotropic effects of lipoprotein apheresis (LA).^{31–33} LA reduces the expression and/or activity of a range of immunocompetent cytokines. CRP, C-reactive protein; DALI, direct adsorption of lipids; IFN, interferon- γ ; IL- α , interleukin- α ; PTX3, pentraxin-3; TNF- α , tumor necrosis factor- α .

LA techniques

Selective methods

Popular adsorption techniques include immunoadsorption (IMA) and dextran sulfate-cellulose-based adsorption (DSA). Both methods require plasma to be separated from blood cells before lipid extraction. In IMA, plasma flows past columns containing antibodies directed at human apoB100. In DSA, columns with dextran sulfate bound to cellulose beads bind very low-density lipoprotein, LDL, and Lp(a) (but not high-density lipoprotein [HDL] in general, but possibly specific forms of it^{41,42}) via electrostatic interaction. The heparin extracorporeal LDL precipitation system precipitates LDL and Lp(a) at low pH. The precipitate is subsequently removed by filtration. Using cascade filtration (CF) or double filtration plasmapheresis, plasma components can be removed using filters with different pore diameters. Large apoB100-containing lipoproteins are removed, whereas small molecules are recovered. Selectivity of CF is, however, limited and HDL and immunoglobulins are also removed.

Both DALI and Liposorber-D work on unseparated whole blood through electrostatic interactions with a polyacrylate-based LDL absorber and dextran sulfate, respectively. HDL and fibrinogen are not significantly affected.

Effectiveness of these methods in lowering LDL-C (about 55%–70% after a single treatment) and Lp(a) mass (50%–60%) is roughly similar.^{25,34,43–45}

Nonselective methods

If selective apheresis facilities are not available, nonselective plasma exchange (PEX) may be considered as a last resort with the understanding that there is risk of antibody induction by non-self peptides. In PEX, whole blood is separated into plasma and cellular components by means of centrifugation or filtration. The cellular components are mixed with albumin solution and saline and given back to the patient. PEX not only eliminates atherogenic lipoproteins from the patient but also other essential plasma proteins such as albumin, immunoglobulins, and coagulation factors.⁴³

Whom to treat with LA

Apheresis facilities are not universally available, and the cost of LA restricts its use to severe, potentially lethal disorders.⁵ In practice, this limits LA use to patients with HoFH, severe refractory HeFH with clinical and image-confirmed CAD, Lp(a) hyperlipoproteinemia with CAD, familial chylomicronemia syndrome, or hypertriglyceridemia with pancreatitis.

Guidelines¹ and local institutional clinical protocols^{26,46} on initiating apheresis treatment have been established. For instance, the Extracorporeal Therapeutic Techniques Unit of the Sapienza University and Umberto I Hospital in Rome, Italy,²⁶ recommends first reaching a genetic and molecular diagnosis (DNA, skin biopsy to enable determination of residual receptor activity of the skin fibroblasts *in vitro*), as well as clinical diagnosis and characterization of the lipoprotein phenotype. In addition to applying noninvasive and invasive cardiovascular techniques, corneal arcus can indicate the presence of atherosclerosis.³ Achilles' tendon width has also been found to correlate with calcific atherosclerosis.⁴⁷ Imaging techniques such as catheterization can help to assess the extent of atherosclerotic disease, both in the diagnostic phase and to monitor disease progression. Currently, stenosis of the coronary arteries and aortic valve can also be assessed with computed tomography (CT) or magnetic resonance imaging of the coronary arteries and aortic valve. CT and magnetic resonance imaging do not exclude catheterization when the treatment adequacy is to be confirmed and/or disease progression is suspected. If plaques are detected, treatment should be started to halt atherogenic progression. If vessels are still not severely affected, treatment may be given biweekly rather than weekly; however, weekly treatment is strongly recommended in HoFH subjects. Serial cardiovascular, cerebrovascular, and peripheral vascular examinations are strongly recommended. CT angiography is the subject of a registry of FH patients, and a recent report has called for CT angiography to be included in clinical trials of interventions in FH to assist in the development of individualized treatment strategies.⁴⁸

Recent data have been published on pregnant women undergoing LA during pregnancy.⁴⁹ The research group found that LA has no unfavorable effects on successful gestation and delivery, and that patients remained compliant with regular therapy. No effects on the fetuses or neonates were detected.⁴⁹ The clinical experience of the author group is that LA can be continued in pregnancy, and that pregnancy-related contra-indications of certain key lipid-lowering drugs mean that for many pregnant women, LA may be the only option for lipid-lowering coverage.

For many patients, the application of apheresis will be governed by access to the treatment. Availability of LA varies markedly across the world, sometimes driven by cost,⁵ sometimes driven by staffing issues, and sometimes driven by cultural, institutional, and medical-specialty attitudes to extracorporeal procedures. For these reasons, we have not included an assessment of the pharmacoeconomic impact of LA.

Clinical experience and side effects

Like any therapy, LA can have adverse effects. The most common side effects are mild-to-severe hypotension and nausea.^{50–52} Venous access problems can also occur.

In a review of more than 4000 LA procedures (IMA, DSA, and DALI systems), LA was found to be effective and safe for long-term use.⁵³ Generally, side effects can be managed well by an expert team. Still, in a minority of patients, they can be debilitating.^{3,25} Long-term side effects may be more frequent using PEX as opposed to LA.⁵⁴

Cyclical rebound effect between apheresis sessions

An inherent drawback of the method is that LDL-C levels undergo a cyclical rebound effect within 1 to 2 weeks, between apheresis procedures (Fig. 3).⁵⁵ In CAD patients treated with atorvastatin, enrolled in the Treating to New Targets trial, higher visit-to-visit variability in LDL-C increased the risk of CVD events (although the data are derived from patients governed by a clinical trial protocol).⁵⁶ The ideal frequency of LA is once weekly.

Attempts should be made to smoothen out the rebound effect between treatments (Fig. 4). To relate the effective extent of LDL-C reduction achieved by LA to recommended lipid and lipoprotein goals, the interval LDL-C levels must be calculated. If the maximum (C_{\max}) and minimum (C_{\min}) LDL-C concentrations that are reached over the course of multiple LA sessions are known, then the predominant method currently used is to calculate mean interval LDL-C levels using the formula: $C_{\text{mean}} = C_{\min} + 0.73(C_{\max} - C_{\min}) \times C_{\min}$, (a coefficient of 0.64 is also frequently used) (Fig. 5).⁵⁵ Considering the mean interval LDL-C reveals the true extent of the dramatic LDL-C reductions achievable with LA.⁵⁵ The utility of mean interval LDL-C values have not been explored extensively in Lp(a).

Combining LA with novel therapies

Alongside the mandated dietary and lifestyle options for patients with dyslipidemias, new classes of lipid-lowering agents (inhibitors of MTP and PCSK9, and mipomersen discussed in the following) may help to attenuate LDL-C rebound between LA sessions.⁵⁷ Obtaining a more “physiological” suppression of LDL-C levels is attempted with “modified” apheresis, which is a term we use to describe the addition of novel lipid-lowering agents to dampen the re-increase of atherogenic lipoproteins in the between-LA interval.

In severe dyslipidemias, combining LA with novel lipid-lowering treatment options may further improve the lipid profile and reduce CVD risk. Combination with more potent therapeutic strategies may allow for a less intense LA therapeutic schedule.⁴ In less severe clinical disease, combination therapy may allow stopping LA altogether, and thus, in some patients, indications may need reconsideration.

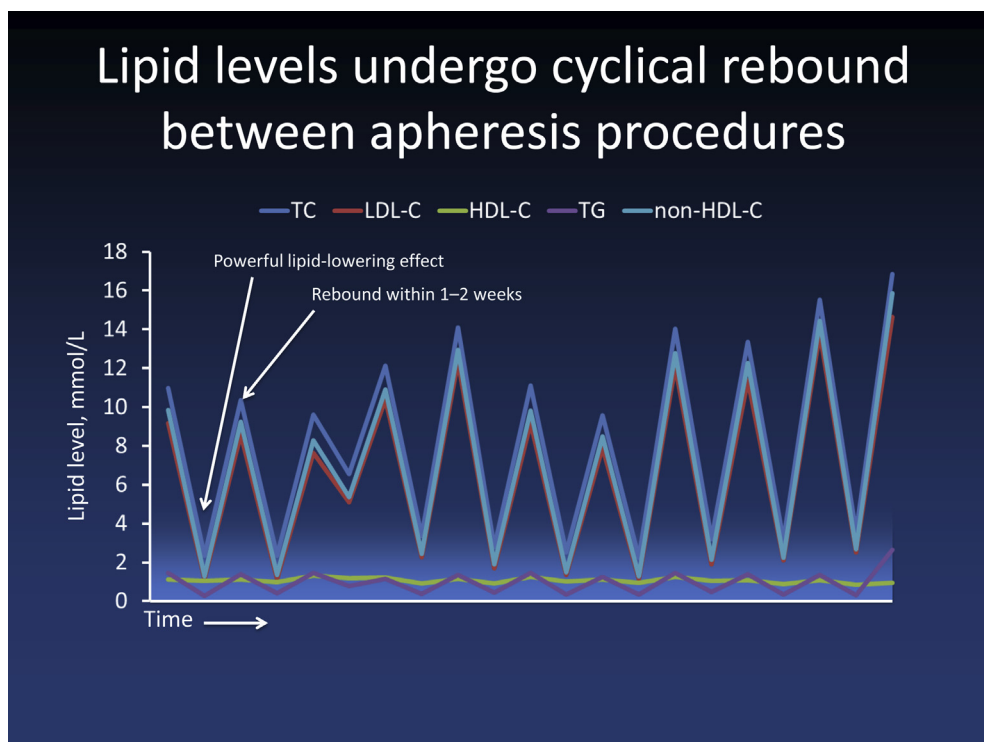


Figure 3 Lipid levels undergo cyclical rebound between apheresis procedures. Representative patient case. HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides.

Novel treatment options

MTP inhibition

Inhibition of microsomal triglyceride transfer protein (MTP) prevents formation of very low-density lipoprotein in the liver and chylomicrons in the intestine. MTP normally transfers triglycerides onto apoB; a necessary step in the formation of apoB-containing lipoproteins, including LDL-C. Lomitapide is the first MTP inhibitor

that has been evaluated as an add-on therapy to statins and a low-fat diet, with or without LA, in patients with HoFH. Most patients achieved effective LDL-C lowering (40%–50%) and achieved LDL-C targets when receiving increasing doses of lomitapide over the course of 26 weeks,⁵⁸ which was sustained out to 126 weeks.⁵⁹ A large variation in treatment responses was observed, which was independent of LDLR function. The mechanism of action of lomitapide can result in hepatic steatosis and gastrointestinal problems (21% of patients). Increased aminotransferase levels $>3\times$ upper limit of normal (34% of patients) and liver fat accumulation $>5.56\%$ (78% of patients) have been reported with lomitapide.^{58,60,61}

Intensive patient guidance and education on adhering to a low-fat diet is important when prescribing lomitapide as this can mitigate the potential issues of steatorrhea. Because transport of fat-soluble vitamin E and essential fatty acids omega 3 and 6 is blocked, these need to be supplemented. Liver enzymes and liver imaging should be performed before and during therapy. In cases of transaminase elevations, dose reduction or interruption and rechallenge have been successful.

PCSK9 inhibition

PCSK9 is a secretory protease that causes degradation of the LDLR. Inhibition of PCSK9 increases recycling of the LDLR back to the hepatocyte surface, thereby promoting LDL clearance. Two monoclonal antibodies directed at

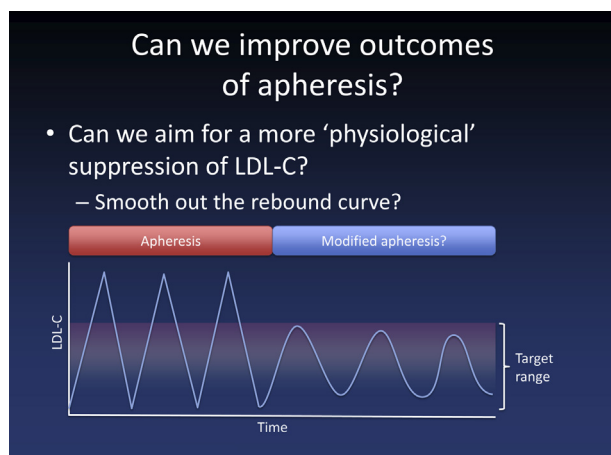


Figure 4 Improving apheresis outcomes. Representative diagram. LDL-C, low-density lipoprotein cholesterol. *Defined as addition of novel lipid-lowering agents to dampen the rebound of atherogenic lipoproteins in the between-LA interval.

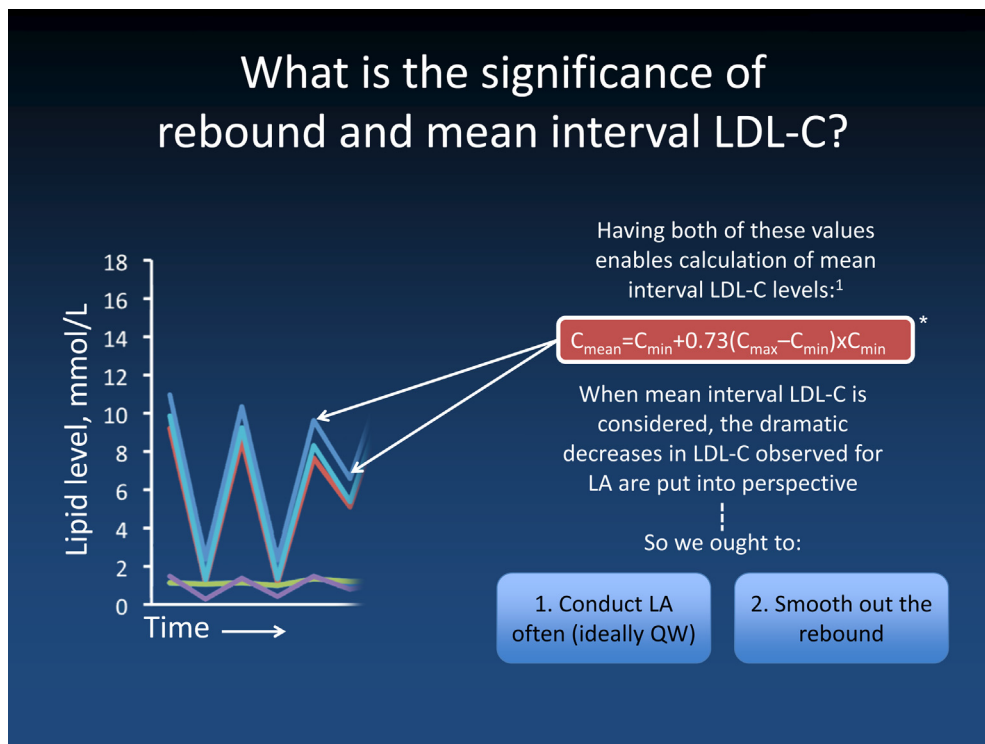


Figure 5 Rebound and calculated mean interval LDL-C govern LA frequency. Mean interval LDL-C calculation⁵⁵ based on representative patient case; *Coefficient of 0.64 is also used. LA, lipoprotein apheresis; LDL-C, low-density lipoprotein cholesterol; QW, once weekly.

PCSK9, evolocumab and alirocumab, have been shown to effectively lower LDL-C and Lp(a) levels in various hypercholesterolemic patient groups, when given in addition to statin and/or ezetimibe therapy.^{62–66} In HeFH patients, decreases in LDL-C were of the order of 40% to 50%, and ~30% in HoFH patients. The effect of inhibiting PCSK9 is dependent on residual LDLR function, and PCSK9 inhibitors do not appear to work in homozygous patients with 2 null LDLR genes.⁶⁷ Genetic testing may help identify patients with receptor-defective mutations. Side effects to PCSK9 inhibitors are rare, apart from mild injection site reactions and flu-like symptoms.^{62,64–66}

A “small interfering RNA” agent is directed against PCSK9 messenger RNA (inclisiran; investigational compound) is in phase II development. Results suggest that the drug can reduce LDL-C levels by 28% to 53% over 180 days.⁶⁸

Antisense therapy targeting apoB

Antisense therapy is generally used to treat genetic disorders or infections. In a genetic disease, antisense drugs are synthesized DNA or RNA that bind to the specific genetic code that underlies the disease. This has the effect of switching the aberrant gene off. Mipomersen is an antisense oligonucleotide agent that targets apoB, and therefore decreases hepatic and plasma levels of apoB and apoCIII. Mipomersen has been approved in the United States since 2013 as an adjunct treatment for patients with HoFH. Clinical studies of mipomersen have shown that the

drug can reduce mean LDL-C and Lp(a) levels by approximately 25% and 31%, respectively.⁶⁹ Common adverse events include injection site reactions (76%) and flu-like symptoms (29%), nausea (18%), headache, (15%), and chest pain (12%).⁶⁹ Mipomersen is not approved in Europe.

HDL mimetics

Observations that apolipoprotein A-1 (apoA-1) and HDL have anti-atherogenic effects have led to development of agents that increase apoA-1 concentrations and HDL particle numbers. In HoFH patients, infusion of a reconstituted apoA-1-containing HDL mimetic resulted in enhanced mobilization of cholesterol into plasma and increased fecal sterol excretion.⁷⁰ These agents remain investigational at present.

Available evidence on integrating LA with new lipid-lowering drugs

We will briefly describe conditions for which LA is indicated, followed by the first emerging evidence on combining LA with pharmacotherapy for each indication.

HoFH—therapeutic options

The latest EAS statement on target levels in HoFH recommends lowering LDL-C in adults to <2.5 mmol/L (100 mg/dL) without clinical CVD, or even to below

1.8 mmol/L (70 mg/dL) in patients with CVD.⁷¹ These targets are very seldom met with currently available pharmacologic therapy. Different criteria have been formulated in different countries on when LA is indicated in HoFH. The ASFA considers the use of LA in HoFH “accepted first-line therapy.”¹

Apheresis combined with statins and ezetimibe

Hitherto, LA combined with high-dose statin and ezetimibe was the most effective means of treating patients with HoFH.⁵⁷ Still, achieving an interval mean LDL-C of 4.2 mmol/L (160 mg/dL) by weekly apheresis plus statin plus ezetimibe therapy failed to prevent progression of aortic, coronary, and carotid disease in HoFH patients who started LA between the ages of 6 and 44 years.²³ Even lower LDL-C levels may be needed to prevent atherosclerotic disease in older patients.

Apheresis combined with PCSK9 inhibitors

An analysis of the Trial Assessing Long Term Use of PCSK9 Inhibition in Subjects with Genetic LDL Disorders (TAUSSIG) study of long-term use of evolocumab in patients with HoFH compared the efficacy of the drug with and without apheresis.⁶³ One hundred and six patients were included in the analysis. All patients were aged >12 years and on stable LDL-lowering therapy. Mean reductions in LDL-C in patients on apheresis were -20.6% at Week 12 ($P = .0012$ compared with baseline), and -23.2 at Week 48 ($P = .0032$). There were no differences between LDL-C reductions between patients receiving apheresis at study entry ($n = 34$) and those who were not ($n = 72$; $P = .38$ at Week 12 and $P = .09$ at Week 48).⁶³

Apheresis combined with MTP inhibition

In a phase III, single-arm, dose-escalating study evaluating lomitapide, 18 of 29 men and women with HoFH who entered a 26-week efficacy phase, regularly received apheresis. During the safety phase (weeks 26–78), 3 patients permanently discontinued apheresis based on their LDL-C response, and in 3 patients, the time interval between sessions was increased.⁵⁸ A post-hoc analysis on data of this study examined how concomitant apheresis affected the lipid-lowering efficacy of lomitapide.⁷² Thirteen of 23 patients who completed the efficacy phase received LA or conventional therapeutic plasmapheresis. Concomitant apheresis did not affect LDL reduction (-48% on apheresis, and -55.1% not receiving apheresis, $P = .545$).

A recent article reports on 7 HoFH patients who were treated with lomitapide in the normal course of their LA therapy (weekly or biweekly), plus statins and ezetimibe.⁴ Lomitapide was uptitrated in individual patients, guided by LDL-lowering effects and adverse events. These observations suggest that when patients are receiving nonmaximal doses (unlike in trial setting), no significant liver fat accumulation is seen. Addition of lomitapide allowed the frequency of LA sessions to be reduced from weekly to biweekly in 3 patients. In 3 others, the LDL-C rebound appeared blunted by addition of lomitapide (Figure 6). Gastrointestinal adverse events were manageable.⁴

Apheresis combined with HDL mimetics

A phase II study evaluating the effect of the recombinant apoA-1 HDL mimetic CER-001 in high-risk subjects with genetically confirmed HoFH on concomitant lipid-lowering treatment, including LA, suggested that it may reverse atherogenic artery wall changes, in the absence of carotid plaque.⁷⁰ In the first hour after CER-001 infusion, apoA-1

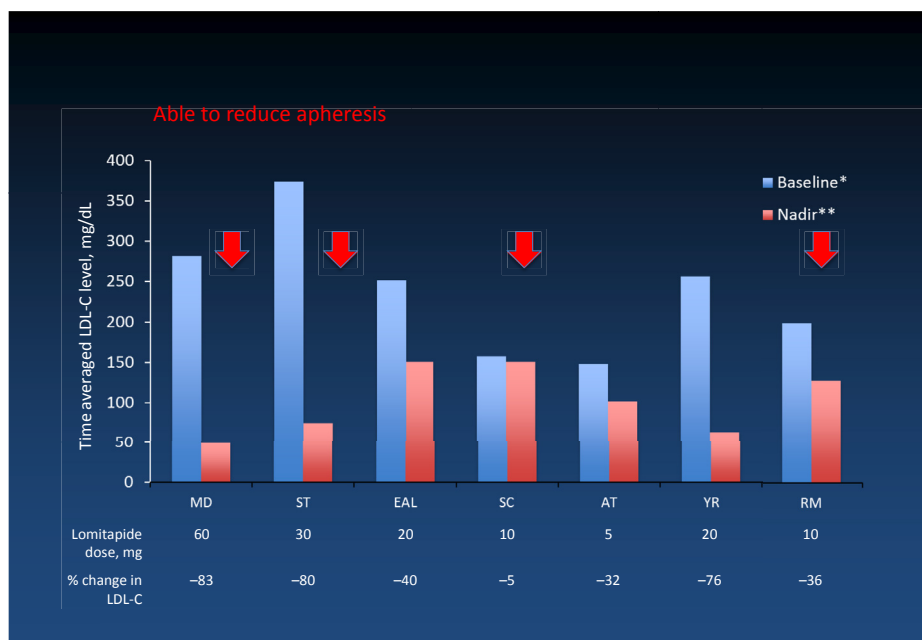


Figure 6 Summary data (time-averaged LDL-C). *Mean of 2–3 pre-lomitapide time averaged LDL-C values. **Lowest recorded time averaged LDL-C level.

levels increased by 13%. No significant changes in TC, HDL-C, and LDL-C were seen, whereas triglyceride levels increased. At baseline, none of the included subjects had overt carotid atherosclerotic plaque. Six months of biweekly infusions with CER-001 resulted in a significant decrease of mean vessel wall area (percentage change from baseline: median: -2.5% , interquartile range: -4.4 to -0.62 , $P = .012$) and a tendency to reduced mean vessel wall thickness (-1.8% , interquartile range: -3.8% to 0.2% , $P = .081$).⁷⁰ HDL mimetics remain investigational.

HeFH—therapeutic options

Statins form the cornerstone of therapy of HeFH patients.^{21,22} There is, however, large interindividual variation in response to treatment, and some patients cannot tolerate statins, particularly at maximal doses.

Apheresis combined with statins and ezetimibe

LA is indicated in some drug-refractory HeFH patients who show progress of CAD or atherosclerosis lesions in other areas (carotids, aorta, and leg arteries). Studies have shown larger LDL-C reductions and regression of coronary lesions or fewer coronary events with apheresis plus drugs than in patients who received only drug therapy.⁵⁰

Apheresis combined with PCSK9 inhibition

For HeFH patients on apheresis, the recent ODYSSEY ESCAPE study examined the benefit of subcutaneously administering the PCSK9 inhibitor alirocumab 150 mg every 2 weeks.⁷³ The primary efficacy endpoint was the rate of apheresis treatments over a 12-week period (Weeks 7–18) between the alirocumab group ($n = 41$) and placebo group ($n = 21$), in whom apheresis schedules were fixed in Weeks 1 to 6. The mean interval change in LDL-C with apheresis is usually in the order of 30%; therefore, patients were not treated with apheresis if their pre-apheresis LDL-C levels were $>30\%$ from a previous treatment. The primary efficacy endpoint demonstrated a 75% reduction in apheresis therapy for the alirocumab group with approximately 64% able to stop apheresis.⁷³ These results show that PCSK9 inhibitors have the potential to significantly reduce or even eradicate the need for apheresis in HeFH patients⁷⁴; however, caution may be required as deletion of LA might lessen beneficial effects on Lp(a) mass.

Lp(a) hyperlipoproteinemia—therapeutic options

Niacin, PCSK9 inhibitors, the CETP inhibitor anacetrapib (investigational), and mipomersen (not approved in Europe) have the potential to lower Lp(a) by approximately 25% to 30%, but the CVD benefit is unknown.^{18,75} The effect of PCSK9 inhibitors in Lp(a) levels is dependent on baseline Lp(a) levels, whereby high baseline Lp(a) (>125 nmol/L) is associated with diminished percentage

reductions and greater absolute reductions compared with lower baseline levels (≤ 125 nmol/L).⁷⁶ Certainly, for these drugs, reduction of Lp(a) levels is generally insufficient. Apo(a) antisense therapy is currently being studied in phase II trials. In a phase I study, Lp(a) was lowered up to 77.8% with the apo(a) antisense therapy ISIS-APO(a). IONIS-APO(a)Rx and its ligand-conjugated variant IONIS-APO(a)LRx have been studied in an ascending-dose phase II trial, in which Lp(a) reductions of up to 72% were achieved with the conjugated drug and with no evidence of injection site reactions or other adverse events of note.⁷⁷

LA can effectively lower Lp(a) levels. For instance, various apheresis techniques (DALI, DSA, heparin extracorporeal LDL precipitation, CF, and PEX) were shown to result in a mean reduction of 71% in Lp(a) levels in 101 hypercholesterolemic patients. Relief of symptoms was seen irrespective of the system used.²⁵ LA removes Lp(a) and LDL simultaneously, which makes it hard to distinguish the effects of Lp(a) and LDL-C lowering.¹⁸ One study bypassed this issue by selecting a group of patients with very high Lp(a) mass levels, who continued to experience a high rate of major adverse coronary events despite effective LDL-C-lowering treatment.^{78,79} Subsequently adding LA, lowered Lp(a) mass by 73% and the rate of major adverse coronary events dramatically reduced by 86% in the 5-year follow-up. At least in these high-risk individuals, lowering levels of Lp(a) mass by LA appears to convey a cardiovascular benefit.⁷⁸ These data have been reviewed in the context of the German national guidelines for LA use.⁸⁰

Specific Lp(a) apheresis using POCARD's Lipopak IMA columns in a cohort of 30 subjects with Lp(a) mass >50 mg/dL and with angiographically verified CHD reduced mean Lp(a) mass from 73 mg/dL to 29 mg/dL over the course of a single treatment. Weekly Lipopak apheresis for 18 months resulted in stable regression of coronary atherosclerosis.⁸¹

No data are available on the effect of combination therapy on Lp(a) mass.

General recommendations: The unmet need for an international registry on LA

Registries provide longitudinal real-world data on the use and outcomes of therapeutic interventions in working clinics. They are established as a major source of post-marketing data for pharmaceuticals and other interventions.

In general, more awareness of both dyslipidemias and the benefits that can be achieved with timely treatment are needed. Educating physicians, including family doctors, should lead to better screening of patients at risk, and referral to a specialist when a genetic dyslipidemia is suspected.

Importantly, more experience needs to be accumulated on when the available treatment options will likely yield most benefit. Documenting the molecular diagnosis and effects of treatment in an international registry will facilitate learning from colleagues' experience, in these rare patients. This registry might follow the example of the German Lipoprotein Apheresis Registry,⁸² which documents LA treatment

procedures, including treatment efficiency, biocompatibility, and clinical safety. After German Lipoprotein Apheresis Registry had been running for 2 years, 96 German centers had access to the registry, 49 centers were active members, and data of more than 700 patients had been entered.⁸³

Other registries devoted to therapeutic hemapheresis, but not specifically focusing on LA, include the World Apheresis Association Apheresis Registry, a registry that captures various kinds of therapeutic apheresis procedures, including collection or removal of blood corpuscles,⁸⁴ and the Apheresis Study Group of the Italian Society of Nephrology, which collects data on a variety of therapeutic apheresis procedures, in 15 Italian regions.^{85,86} Evidence-based guidelines are periodically released by the ASFA.¹

An international registry devoted to LA can accumulate data on rare patients who are being treated with nonstandard treatment regimens, relatively quickly. This will allow invaluable analyses and yield much-needed clinical insight on how to optimally treat dyslipidemic patients at high CVD risk. The need for registries is also highlighted by the fact that randomized clinical trials with LA are extremely difficult for ethical reasons.

Conclusion

Although many important advances are being made in the field of lipid-lowering therapy, many dyslipidemic patients still do not attain sufficient lipid lowering, and, as a result, they remain at high CVD risk. Novel lipid-lowering agents may be promising to further reduce CVD risk if conventional therapies do not yield adequate results, with or without LA. However, to date, the only published evidence on combination therapy of LA with novel therapeutic options is on lomitapide, alirocumab, and CER-001. Thus, more studies on combining LA with inhibitors of PCSK9 or apoB synthesis and other novel lipid-lowering strategies in development are highly warranted. Our review is the first comprehensive attempt to provide recommendations to integrate novel lipid-lowering therapies with LA in severe, chronic dyslipidemias.

To accelerate the expansion of the clinical experience and body of evidence, data on patient characteristics and chosen treatment strategies and effects should be documented in an international registry. The Multidisciplinary International Group for Hemapheresis Therapy and Metabolic Disturbances Contrast (Mighty Medic) Working Group aims to play an important role in accomplishing this. Mighty Medic hopes to contribute by publishing regularly updated concrete proposals for an international consensus on LA, covering known and new indications, how to deal with special patient groups, and what can be achieved with combination therapy with novel drugs. Moreover, Mighty Medic will set up the proposed international registry on LA, network with sister societies (International Society for Apheresis, ASFA, World Apheresis Association), and other scientific societies focused on these arguments such as the International Atherosclerosis

Society, National Lipid Association and Lipid-Liga, Italian Society of Nephrology, Italian Society of Hemapheresis, and facilitate multicenter scientific collaborations on genetic, mechanistic, and pooled case studies.

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References

1. Schwartz J, Padmanabhan A, Aquilino N, et al. Guidelines on the use of therapeutic apheresis in clinical practice—evidence-based approach from the Writing Committee of the American Society for Apheresis: the Seventh Special Issue. *J Clin Apher.* 2016;31:149–162.
2. Watts GF, Gidding S, Wierzbicki AS, et al. Integrated guidance on the care of familial hypercholesterolaemia from the International FH Foundation. *Int J Cardiol.* 2014;171:309–325.
3. Cuchel M, Bruckert E, Ginsberg HN, et al. European Atherosclerosis Society Consensus Panel on Familial H. Homozygous familial hypercholesterolaemia: new insights and guidance for clinicians to improve detection and clinical management. A position paper from the Consensus Panel on Familial Hypercholesterolaemia of the European Atherosclerosis Society. *Eur Heart J.* 2014;35:2146–2157.
4. Stefanutti C, Morozzi C, Di Giacomo S, Sovrano B, Mesce D, Grossi A. Management of homozygous familial hypercholesterolemia in real-world clinical practice: a report of 7 Italian patients treated in Rome with lomitapide and lipoprotein apheresis. *J Clin Lipidol.* 2016;10:782–789.
5. Wang A, Richhariya A, Gandra SR, et al. Systematic review of low-density lipoprotein cholesterol apheresis for the treatment of familial hypercholesterolemia. *J Am Heart Assoc.* 2016;5. <http://dx.doi.org/10.1161/JAHA.116.003294>.
6. France M, Rees A, Datta B, et al. HEART UK statement on the management of homozygous familial hypercholesterolaemia in the United Kingdom. *Atherosclerosis.* 2016;255:128–139.
7. Santos RD, Gidding SS, Hegele RA, et al. International Atherosclerosis Society Severe Familial Hypercholesterolemia P. Defining severe familial hypercholesterolaemia and the implications for clinical management: a consensus statement from the International Atherosclerosis Society Severe Familial Hypercholesterolemia Panel. *Lancet Diabetes Endocrinol.* 2016;4:850–861.
8. Zech LA Jr, Hoeg JM. Correlating corneal arcus with atherosclerosis in familial hypercholesterolemia. *Lipids Health Dis.* 2008;7:7.
9. Sjouke B, Hovingh GK, Kastelein JJ, Stefanutti C. Homozygous autosomal dominant hypercholesterolemia: prevalence, diagnosis, and current and future treatment perspectives. *Curr Opin Lipidol.* 2015;26:200–209.

10. Gautschi M, Pavlovic M, Nuoffer JM. Fatal myocardial infarction at 4.5 years in a case of homozygous familial hypercholesterolaemia. *JIMD Rep.* 2012;2:45–50.
11. Huijgen R, Hutten BA, Kindt I, Vissers MN, Kastelein JJ. Discriminative ability of LDL-cholesterol to identify patients with familial hypercholesterolemia: a cross-sectional study in 26,406 individuals tested for genetic FH. *Circ Cardiovasc Genet.* 2012;5:354–359.
12. Marshall WJ, Bangert SK, Lapsley M. *Clinical Chemistry.* St. Louis, MO: Mosby; 2012.
13. Boffa MB, Koschinsky ML. Screening for and management of elevated Lp(a). *Curr Cardiol Rep.* 2013;15:417.
14. Brown WV, Moriarty PM, Remaley AT, Tsimikas S. JCL roundtable: should we treat elevations in Lp(a)? *J Clin Lipidol.* 2016;10:215–224.
15. Koschinsky ML. Novel insights into Lp(a) physiology and pathogenicity: more questions than answers? *Cardiovasc Hematol Disord Drug Targets.* 2006;6:267–278.
16. Marcovina SM, Koschinsky ML. A critical evaluation of the role of Lp(a) in cardiovascular disease: can Lp(a) be useful in risk assessment? *Semin Vasc Med.* 2002;2:335–344.
17. Yeang C, Witztum JL, Tsimikas S. 'LDL-C' = LDL-C + Lp(a)-C: implications of achieved ultra-low LDL-C levels in the proprotein convertase subtilisin/kexin type 9 era of potent LDL-C lowering. *Curr Opin Lipidol.* 2015;26:169–178.
18. Kronenberg F, Utermann G. Lipoprotein(a): resurrected by genetics. *J Intern Med.* 2013;273:6–30.
19. Qin SY, Liu J, Jiang HX, Hu BL, Zhou Y, Olkkonen VM. Association between baseline lipoprotein (a) levels and restenosis after coronary stenting: meta-analysis of 9 cohort studies. *Atherosclerosis.* 2013;227:360–366.
20. Nordestgaard BG, Chapman MJ, Ray K, et al. European Atherosclerosis Society Consensus P. Lipoprotein(a) as a cardiovascular risk factor: current status. *Eur Heart J.* 2010;31:2844–2853.
21. Stone NJ, Robinson JG, Lichtenstein AH, et al. American College of Cardiology/American Heart Association Task Force on Practice G. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation.* 2014;129:S1–S45.
22. Jacobson TA, Ito MK, Maki KC, et al. National Lipid Association recommendations for patient-centered management of dyslipidemia: part 1-executive summary. *J Clin Lipidol.* 2014;8:473–488.
23. Graesdal A, Bogsrud MP, Holven KB, et al. Apheresis in homozygous familial hypercholesterolemia: the results of a follow-up of all Norwegian patients with homozygous familial hypercholesterolemia. *J Clin Lipidol.* 2012;6:331–339.
24. Stasiewski E, Christoph M, Christoph A, Bittner A, Weidner K, Julius U. Mental symptoms and quality of life in lipoprotein apheresis patients in comparison to hemodialysis patients, platelet donors and normal population. *Atheroscler Suppl.* 2015;18:233–240.
25. Stefanutti C, Morozzi C, Di Giacomo S, Italian Multicenter Study on Low-Density Lipoprotein Apheresis Working G. Italian multicenter study on low-density lipoprotein apheresis Working Group 2009 survey. *Ther Apher Dial.* 2013;17:169–178.
26. Stefanutti C, Vivenzio A, Di Giacomo S, Mazzarella B, Bosco G, Berni A. Aorta and coronary angiographic follow-up of children with severe hypercholesterolemia treated with low-density lipoprotein apheresis. *Transfusion.* 2009;49:1461–1470.
27. Schuff-Werner P, Fenger S, Kohlschein P. Role of lipid apheresis in changing times. *Clin Res Cardiol Suppl.* 2012;7:7–14.
28. Thompson GR. The evidence-base for the efficacy of lipoprotein apheresis in combating cardiovascular disease. *Atheroscler Suppl.* 2013;14:67–70.
29. Thompson GR, Miller JP, Breslow JL. Improved Survival of Patients With Homozygous Familial Hypercholesterolaemia Treated With Plasma Exchange. *Br Med J (J Clin Res Ed).* 1985;291:1671–1673.
30. Bruckert E, Saheb S, Bonté JR, Coudray-Omnès C. Daily life, experience and needs of persons suffering from homozygous familial hypercholesterolaemia: insights from a patient survey. *Atheroscler Suppl.* 2014;15:46–51.
31. Stefanutti C, Vivenzio A, Di Giacomo S, Ferraro PM. Cytokines profile in serum of homozygous familial hypercholesterolemia is changed by LDL-apheresis. *Cytokine.* 2011;55:245–250.
32. Hovland A, Hardersen R, Sexton J, Mollnes TE, Lappegaard KT. Different inflammatory responses induced by three LDL-lowering apheresis columns. *J Clin Apher.* 2009;24:247–253.
33. van Wijk DF, Sjouke B, Figueroa A, et al. Nonpharmacological lipoprotein apheresis reduces arterial inflammation in familial hypercholesterolemia. *J Am Coll Cardiol.* 2014;64:1418–1426.
34. Arai K, Orsoni A, Mallat Z, et al. Acute impact of apheresis on oxidized phospholipids in patients with familial hypercholesterolemia. *J Lipid Res.* 2012;53:1670–1678.
35. Julius U, Milton M, Stoellner D, et al. Effects of lipoprotein apheresis on PCSK9 levels. *Atheroscler Suppl.* 2015;18:180–186.
36. Schettler V, Methe H, Staschinsky D, Schuff-Werner P, Muller GA, Wieland E. Review: the oxidant/antioxidant balance during regular low density lipoprotein apheresis. *Ther Apher.* 1999;3:219–226.
37. Moriarty PM, Hemphill L. Lipoprotein apheresis. *Cardiol Clin.* 2015; 33:197–208.
38. Stefanutti C, Mazza F, Steiner M, et al. Relationship between sustained reductions in plasma lipid and lipoprotein concentrations with apheresis and plasma levels and mRNA expression of PTX3 and plasma levels of hsCRP in patients with hyperLp(a) lipoproteinemia. *Mediators Inflamm.* 2016;2016:4739512.
39. Tavori H, Giunzioni I, Linton MF, Fazio S. Loss of plasma proprotein convertase subtilisin/kexin 9 (PCSK9) after lipoprotein apheresis. *Circ Res.* 2013;113:1290–1295.
40. Hori M, Ishihara M, Yuasa Y, et al. Removal of plasma mature and furin-cleaved proprotein convertase subtilisin/kexin 9 by low-density lipoprotein-apheresis in familial hypercholesterolemia: development and application of a new assay for PCSK9. *J Clin Endocrinol Metab.* 2015;100:E41–E49.
41. Moriarty PM, Luyendyk JP, Gibson CA, Backes JM. Effect of low-density lipoprotein apheresis on plasma levels of apolipoprotein e4. *Am J Cardiol.* 2010;105:1585–1587.
42. Opole IO, Belmont JM, Kumar A, Moriarty PM. Effect of low-density lipoprotein apheresis on inflammatory and noninflammatory high-density lipoprotein cholesterol. *Am J Cardiol.* 2007;100:1416–1418.
43. Winters JL. Lipid apheresis, indications, and principles. *J Clin Apher.* 2011;26:269–275.
44. Julius U, Fischer S, Schatz U, Hohenstein B, Bornstein S. Lipoprotein apheresis: an update. *Clin Lipidol.* 2013;8:693–705.
45. Julius U, Fischer S, Schatz U, Passauer J, Bornstein S. Why an apheresis center should offer more than one lipoprotein apheresis method. *Ther Apher Dial.* 2013;17:179–184.
46. Schettler V, Neumann CL, Hulpke-Wette M, Hagenah GC, Schulz EG, Wieland E, German Apheresis Working G. Current view: indications for extracorporeal lipid apheresis treatment. *Clin Res Cardiol Suppl.* 2012;7:15–19.
47. Raal FJ, Santos RD. Homozygous familial hypercholesterolemia: current perspectives on diagnosis and treatment. *Atherosclerosis.* 2012; 223:262–268.
48. Sijbrands EJ, Nieman K, Budoff MJ, Consortium FC. Cardiac computed tomography imaging in familial hypercholesterolaemia: implications for therapy and clinical trials. *Curr Opin Lipidol.* 2015;26:586–592.
49. Ogura M, Makino H, Kamiya C, et al. Lipoprotein apheresis is essential for managing pregnancies in patients with homozygous familial hypercholesterolemia: seven case series and discussion. *Atherosclerosis.* 2016;254:179–183.
50. Stefanutti C, Julius U. Lipoprotein apheresis: state of the art and novelties. *Atheroscler Suppl.* 2013;14:19–27.
51. Heigl F, Hettich R, Lotz N, et al. Efficacy, safety, and tolerability of long-term lipoprotein apheresis in patients with LDL- or Lp(a) hyperlipoproteinemia: findings gathered from more than 36,000 treatments at one center in Germany. *Atheroscler Suppl.* 2015;18:154–162.
52. Dittrich-Riediger J, Schatz U, Hohenstein B, Julius U. Adverse events of lipoprotein apheresis and immunoabsorption at the Apheresis Center at the University Hospital Dresden. *Atheroscler Suppl.* 2015;18:45–52.

53. Bambauer R, Schiel R, Latza R. Low-density lipoprotein apheresis: an overview. *Ther Apher Dial*. 2003;7:382–390.
54. Health Quality Ontario. Low-density lipoprotein apheresis: an evidence-based analysis. *Ont Health Technol Assess Ser*. 2007;7:1–101.
55. Kroon AA, van't Hof MA, Demacker PN, Stalenhoef AF. The rebound of lipoproteins after LDL-apheresis. Kinetics and estimation of mean lipoprotein levels. *Atherosclerosis*. 2000;152:519–526.
56. Bangalore S, Breazna A, DeMicco DA, Wun CC, Messerli FH, Committee TNTS and Investigators. Visit-to-visit low-density lipoprotein cholesterol variability and risk of cardiovascular outcomes: insights from the TNT trial. *J Am Coll Cardiol*. 2015;65:1539–1548.
57. Stefanutti C, Thompson GR. Lipoprotein apheresis in the management of familial hypercholesterolaemia: historical perspective and recent advances. *Curr Atheroscler Rep*. 2015;17:465.
58. Cuchel M, Meagher EA, du Toit Theron H, et al, Phase 3 Ho FHLSI. Efficacy and safety of a microsomal triglyceride transfer protein inhibitor in patients with homozygous familial hypercholesterolaemia: a single-arm, open-label, phase 3 study. *Lancet*. 2013;381:40–46.
59. Blom DJ, Averna M, Meagher EA, et al. Long-term Efficacy and Safety of Lomitapide for the Treatment of Homozygous Familial Hypercholesterolemia: Results of the Phase 3 Extension Trial. Orlando, Florida: Paper presented at: AHA; 2015.
60. Aegerion Pharmaceuticals Inc. Lojuxta Summary of Product Characteristics. 2015 Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002578/human_med_001668.jsp&mid=WC0b01ac058001d124.
61. Cuchel M, Bloedon LT, Szapary PO, et al. Inhibition of microsomal triglyceride transfer protein in familial hypercholesterolemia. *N Engl J Med*. 2007;356:148–156.
62. Raal FJ, Honarpour N, Blom DJ, et al, Investigators T. Inhibition of PCSK9 with evolocumab in homozygous familial hypercholesterolaemia (TESLA Part B): a randomised, double-blind, placebo-controlled trial. *Lancet*. 2015;385:341–350.
63. Raal FJ, Hovingh GK, Blom D, et al. Long-term treatment with evolocumab added to conventional drug therapy, with or without apheresis, in patients with homozygous familial hypercholesterolaemia: an interim subset analysis of the open-label TAUSSIG study. *Lancet Diabetes Endocrinol*. 2017;5:280–290.
64. Zhang XL, Zhu QQ, Zhu L, et al. Safety and efficacy of anti-PCSK9 antibodies: a meta-analysis of 25 randomized, controlled trials. *BMC Med*. 2015;13:123.
65. Robinson JG, Farnier M, Krempf M, et al. Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. *N Engl J Med*. 2015;372:1489–1499.
66. Cannon CP, Cariou B, Blom D, et al. Efficacy and safety of alirocumab in high cardiovascular risk patients with inadequately controlled hypercholesterolaemia on maximally tolerated doses of statins: the ODYSSEY COMBO II randomized controlled trial. *Eur Heart J*. 2015;36:1186–1194.
67. Stein EA, Honarpour N, Wasserman SM, Xu F, Scott R, Raal FJ. Effect of the proprotein convertase subtilisin/kexin 9 monoclonal antibody, AMG 145, in homozygous familial hypercholesterolemia. *Circulation*. 2013;128:2113–2120.
68. Ray KK, Landmesser U, Leiter LA, et al. Inclisiran in patients at high cardiovascular risk with elevated LDL cholesterol. *N Engl J Med*. 2017;376:1430–1440.
69. Raal FJ, Santos RD, Blom DJ, et al. Mipomersen, an apolipoprotein B synthesis inhibitor, for lowering of LDL cholesterol concentrations in patients with homozygous familial hypercholesterolaemia: a randomised, double-blind, placebo-controlled trial. *Lancet*. 2010;375:998–1006.
70. Hovingh GK, Smits LP, Stefanutti C, et al. The effect of an apolipoprotein A-I-containing high-density lipoprotein-mimetic particle (CER-001) on carotid artery wall thickness in patients with homozygous familial hypercholesterolemia: the Modifying Orphan Disease Evaluation (MODE) study. *Am Heart J*. 2015;169:736–742.e1.
71. Catapano AL, Graham I, De Backer G, et al, Authors/Task Force M and Additional C. 2016 ESC/EAS Guidelines for the management of dyslipidaemias: the Task Force for the Management of Dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J*. 2016;37:2999–3058.
72. Stefanutti C, Blom DJ, Averna MR, et al, Phase 3 Ho FHLSI. The lipid-lowering effects of lomitapide are unaffected by adjunctive apheresis in patients with homozygous familial hypercholesterolaemia - A post-hoc analysis of a Phase 3, single-arm, open-label trial. *Atherosclerosis*. 2015;240:408–414.
73. Moriarty PM, Parhofer KG, Babirak SP, et al. Alirocumab in patients with heterozygous familial hypercholesterolaemia undergoing lipoprotein apheresis: the ODYSSEY ESCAPE trial. *Eur Heart J*. 2016;37:3588–3595.
74. Watts GF, Stefanutti C. ODYSSEY ESCAPE: is PCSK9 inhibition the Trojan Horse for the use of lipoprotein apheresis in familial hypercholesterolaemia? *Eur Heart J*. 2016;37:3596–3599.
75. Stein EA, Raal F. Future directions to establish lipoprotein(a) as a treatment for atherosclerotic cardiovascular disease. *Cardiovasc Drugs Ther*. 2016;30:101–108.
76. Raal FJ, Giugliano RP, Sabatine MS, et al. Reduction in lipoprotein(a) with PCSK9 monoclonal antibody evolocumab (AMG 145): a pooled analysis of more than 1300 patients in 4 phase II trials. *J Am Coll Cardiol*. 2014;63:1278–1288.
77. Viney NJ, van Capelleveveen JC, Geary RS, et al. Antisense oligonucleotides targeting apolipoprotein(a) in people with raised lipoprotein(a): two randomised, double-blind, placebo-controlled, dose-ranging trials. *Lancet*. 2016;388:2239–2253.
78. Jaeger BR, Richter Y, Nagel D, et al, Seidel D and Group of Clinical I. Longitudinal cohort study on the effectiveness of lipid apheresis treatment to reduce high lipoprotein(a) levels and prevent major adverse coronary events. *Nat Clin Pract Cardiovasc Med*. 2009;6:229–239.
79. Roeseler E, Julius U, Heigl F, et al, ProLiFe-Study G. Lipoprotein apheresis for lipoprotein(a)-associated cardiovascular disease: prospective 5 years of follow-up and apolipoprotein(a) characterization. *Arterioscler Thromb Vasc Biol*. 2016;36:2019–2027.
80. Klingel R, Heibges A, Fassbender C, ProLiFe-Study G. Prevention of cardiovascular complications in patients with Lp(a)-hyperlipoproteinemia and progressive cardiovascular disease by long-term lipoprotein apheresis according to German national guidelines. *Clin Res Cardiol Suppl*. 2017;12:38–43.
81. Safarova MS, Ezhov MV, Afanasieva OI, et al. Effect of specific lipoprotein(a) apheresis on coronary atherosclerosis regression assessed by quantitative coronary angiography. *Atheroscler Suppl*. 2013;14:93–99.
82. Nestruck AC, Davignon J. Risks for hyperlipidemia. *Cardiol Clin*. 1986;4:47–56.
83. Schettler VJ, Neumann CL, Peter C, et al, Scientific Board of GftGAWG. First data from the German Lipoprotein Apheresis Registry (GLAR). *Atheroscler Suppl*. 2015;18:41–44.
84. Association WA. New World Apheresis Association Apheresis Registry. 2016 Available at: <http://worldapheresis.org/>.
85. Passalacqua S, Staffolani E, Busnach G, et al, Apheresis Study Group of the Italian Society of N. The Italian Registry for Therapeutic Apheresis. A report from the Apheresis Study Group of the Italian Society of Nephrology. *J Clin Apher*. 2005;20:101–106.
86. De Silvestro G, Bagatella P, Vicarioto M, Tison T, Marson P. The Italian SIdEM registry for apheresis: an overview of the 2005 statistics. *Int J Artif Organs*. 2008;31:354–362.
87. Sjouke B, Kusters DM, Kindt I, et al. Homozygous autosomal dominant hypercholesterolaemia in the Netherlands: prevalence, genotype-phenotype relationship, and clinical outcome. *Eur Heart J*. 2015;36:560–565.
88. Do R, Stitzel NO, Won HH, et al. Exome sequencing identifies rare LDLR and APOA5 alleles conferring risk for myocardial infarction. *Nature*. 2015;518:102–106.
89. Benn M, Watts GF, Tybjaerg-Hansen A, Nordestgaard BG. Familial hypercholesterolemia in the Danish general population: prevalence, coronary artery disease, and cholesterol-lowering medication. *J Clin Endocrinol Metab*. 2012;97:3956–3964.

Appendix 1. Evidence grading according to the Writing Committee of the American Society for Apheresis¹

Table A1 Indications for therapeutic apheresis—ASFA 2016 categories

Category	Description
I	Disorders for which apheresis is accepted as first-line therapy, either as a primary stand-alone treatment or in conjunction with other modes of treatment. <i>Example: plasma exchange in Guillain-Barre syndrome as first-line stand-alone therapy; plasma exchange in myasthenia gravis as first-line in conjunction with immunosuppression and cholinesterase inhibition</i>
II	Disorders for which apheresis is accepted as second-line therapy, either as a stand-alone treatment or in conjunction with other modes of treatment. <i>Example: plasma exchange as stand-alone secondary treatment for acute disseminated encephalomyelitis after high-dose IV corticosteroid failure; extracorporeal photopheresis added to corticosteroids for unresponsive chronic graft-versus-host disease</i>
III	Optimum role of apheresis therapy is not established. Decision-making should be individualized. <i>Example: extracorporeal photopheresis for nephrogenic systemic fibrosis; plasma exchange in patients with sepsis and multi-organ failure</i>
IV	Disorders in which published evidence demonstrates or suggests apheresis to be ineffective or harmful. Institutional Review Board approval is desirable if apheresis treatment is undertaken in these circumstances. <i>Example: plasma exchange for active rheumatoid arthritis</i>

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Table A2 Grading recommendations

Recommendation	Description	Methodological quality of supporting evidence	Implications
Grade 1A	Strong recommendation, high-quality evidence	RCTs without important limitations or overwhelming evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
Grade 1B	Strong recommendation, moderate quality evidence	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Strong recommendation can apply to most patients in most circumstances without reservation
Grade 1C	Strong recommendation, low-quality, or very low-quality evidence	Observational studies or case series	Strong recommendation but may change when higher quality evidence becomes available
Grade 2A	Weak recommendation, high-quality evidence	RCTs without important limitations or overwhelming evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or values of patients or society
Grade 2B	Weak recommendation, moderate-quality evidence	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or values of patients or society
Grade 2C	Weak recommendation, low-quality or very low-quality evidence	Observational studies or case series	Very weak recommendations: other alternatives may be equally reasonable

RCTs, randomized clinical trials.

These recommendations are those provided by ASFA and were used to apply gradings to the combination therapies described in this review.

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Table A3 Data sheet—familial hypercholesterolemia

Incidence	Condition	Procedure	Recommendation	Category
Homozygotes: 1/1,000,000/y [§]	Homozygotes*	LDL apheresis	Grade 1A	I
Heterozygotes: 200/100,000/y	Heterozygotes	LDL apheresis	Grade 1A	II
	Homozygotes with small blood volume [†]	TPE	Grade 1C	II
Number of reported patients*: >300, number of studies (number of patients [‡])				
Report type	RCT	CT	CS	CR
LDL apheresis	6 (228)	15 (308)	22 (401)	NA
TPE	0	1 (5)	14 (62)	NA

CR, case report; CS, case series; CT, clinical trial; LDL, low-density lipoprotein; NA, not applicable; RCT, randomized clinical trial; TPE, therapeutic plasma exchange.^{87–89}

*Approved indications vary among countries.

[†]Relative to manufacturers' recommendation for available selective removal devices.

[‡]Total number enrolled regardless of treatment assignment.

[§]Recent estimates place incidence higher (Sjouke B et al., *Eur Heart J* 2015; 36:560-5).

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* MIGHTY MEDIC: Multidisciplinary International Group for Hemapheresis Therapy and Metabolic Disorders Control.