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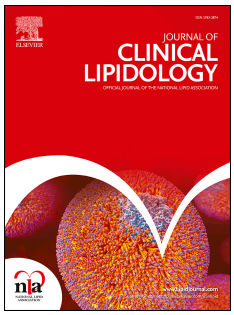

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Towards an international consensus – integrating lipoprotein apheresis and new lipid-lowering drugs

Claudia Stefanutti[1]*, Ulrich Julius[2], Gerald F Watts[3], Mariko Harada-Shiba[4], Maria Cossu[5], Volker J Schettler[6], Giustina De Silvestro[7], Handrean Soran[8], Jeanine Roeters Van Lennep[9], Livia Pisciotta[10], Hans U Klör[11], Kurt Widhalm[12] Patrick M Moriarty[13] and the MIGHTY MEDIC Multinational Society (see Appendix 2 for the composition of group)

Affiliations

[1]Extracorporeal Therapeutic Techniques Unit, Lipid Clinic and Atherosclerosis Prevention Centre, Immunohematology and Transfusion Medicine, Department of Molecular Medicine, 'La Sapienza' University of Rome, 'Umberto I' Hospital, Piazzale Aldo Moro 5, 00185Rome, Italy, claudia.stefanutti@uniroma1.it

[2]Department of Internal Medicine III, University Hospital Carl Gustav Carus at the TechnischeUniversität Dresden, Fetscherstraße 74, 01307 Dresden, Germany, ulrich.Julius@uniklinikum-dresden.de

[3]Lipid Disorders Clinic, Department of Cardiology, Royal Perth Hospital, School of Medicine and Pharmacology, University of Western Australia, 35 Stirling Highway, Crawley WA 6009, Australia, gerald.watts@uwa.edu.au

[4]Department of Molecular Innovation in Lipidology, National Cerebral and Cardiovascular Center Research Institute, 5-7-1 Fujishiro-dai, Suita, Osaka 565-8565, Japan, mshiba@ncvc.go.jp

[5]Struttura Complessa Nefrologia Dialisi e Trapianto, Ospedale "SS. Annunziata", Azienda Ospedalier Universitaria, Sassari, Italy, maria.cossu@aousassari.it

[6]Center of Nephrology GoettingenGbR, An der Lutter 24, 37075 Göttingen, Germany, v.schettler@nz-goe.de

[7]Serv. Immunoematologia e Trasfusionale Azienda Ospedaliera Università di Padova, Via Giustiniani 2 Padova, Italy, giustina.desilvestro@sanita.pad

[8]University Department of Acute Medicine, Manchester Royal Infirmary, Central Manchester University Hospitals, Oxford Road, Manchester, M13 9WLManchester, United Kingdom, handrean.soran@cmmc.nhs.uk

[9]Dept. Internal Medicine, Erasmus MC, 's-Gravendijkwal 230, 3015 CE Rotterdam, The Netherlands, j.roetersvanlennep@erasmusmc.nl

[10]IRCCS AOU San Martino-IST, Department of Internal Medicine, University of Genoa, Italy

[11]DGFF Lipid-Ligae.V. MörfelderLandstraße 72, Frankfurt am Main, Hessen, 60598 Deutschland

[12]Academic Institute for Clinical Nutrition, Alserstraße 14/4a, A-1090, Vienna, Austria

[13]Department of Internal Medicine, Division of Clinical Pharmacology, University of Kansas Medical Center, 3901 Rainbow Boulevard, Kansas City, KS 66160, USA, pmoriart@kumc.edu

*Corresponding author email: claudia.stefanutti@uniroma1.it

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Running title

Lipoprotein apheresis

Abstract

Background

Despite advances in pharmacotherapy of lipid disorders, many dyslipidemic patients do not attain sufficient lipid-lowering to mitigate risk of atherosclerotic cardiovascular disease (ASCVD). Several classes of novel lipid-lowering agents are being evaluated to reduce ASCVD 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 PCSK9 or MTP, HDL 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 (HoFH) and alirocumab/evolocumab in heterozygous familial hypercholesterolemia (HeFH) 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 (MIGHTY MEDIC) 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 CVD risk.

Word count 250; limit 250

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 manuscript and abstract form, and applied evidence grades thereon (Box 1).[2] Grades were applied according to 80% consensus among the author panel.

Box 1

Levels of evidence

1 = systematic review/meta-analysis/at least one 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

1. **Homozygous familial hypercholesterolemia (HoFH)**
   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 EAS 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 PCSK9 inhibitors are probably effective. (2B)

1.3.2. If a patient has two null mutations, and therefore no remaining LDLR activity, or has ARH, 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)

2. **Heterozygous familial hypercholesterolemia (HeFH)**

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 HoFH 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).

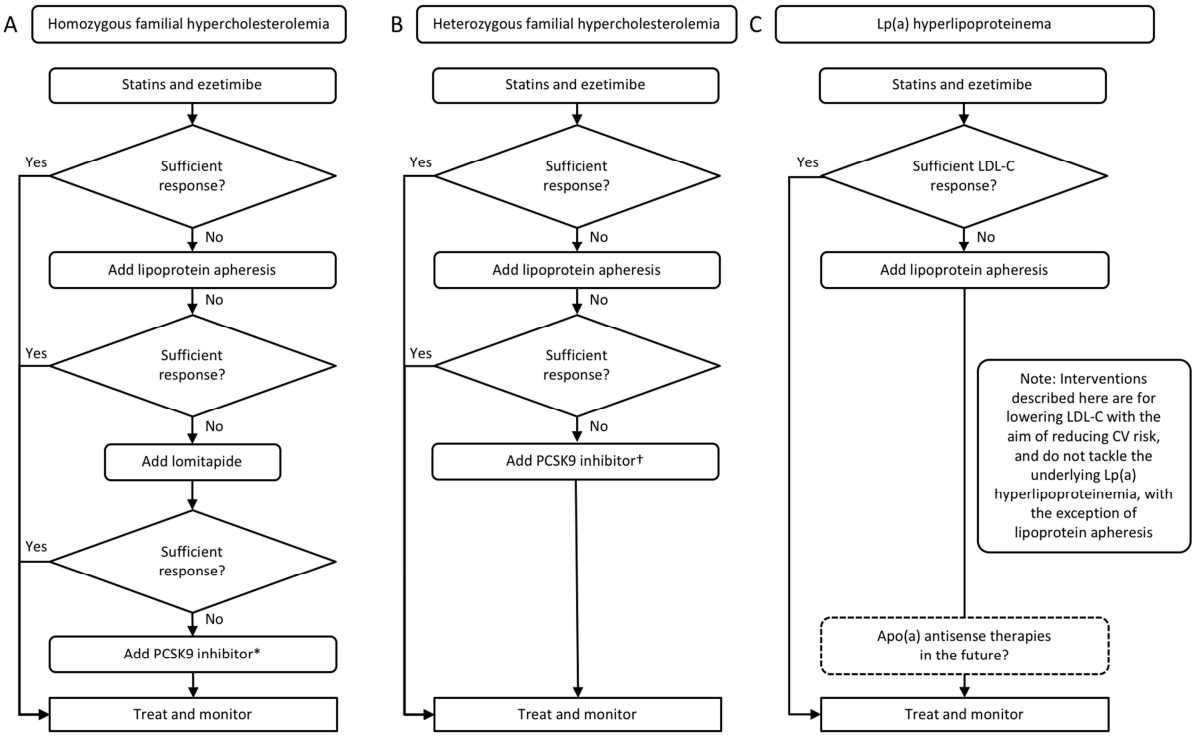
3.1. Lp(a) mass should be measured once in all subjects at intermediate or high risk of CVD/CHD who present with premature CVD, FH, a family history of premature CVD without elevated LDL-C levels or recurrent CVD despite statin treatment. (1A)

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/day) 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)

Figure 1. Treatment algorithm for (A) HoFH, (B) HeFH and (C) Lp(a) hyperlipoproteinemia



Legend: *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; PSCK9, 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.

The most important concept underlying treatment of mono- 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 ASFA,[1] and for familial hypercholesterolemia (FH) by the International FH foundation.[2] The EAS issues general guidance for the treatment of HoFH,[6] and HEART UK has also issued guidance on HoFH, which includes use of LA.[7] Additionally, a recent consensus panel has developed guidance for phenotypic diagnosis of HoFH.[8]

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 lipoprotein apheresis

Homozygous familial hypercholesterolemia (HoFH)

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).[8, 9]

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), PCSK9 (*PCSK9*: OMIM #607786) or the LDLR adaptor protein 1 (*LDLRAP1* or *ARH* for autosomal recessive hypercholesterolemia, OMIM# 605747).[10] 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 onwards. Case reports have described extensive atherosclerotic vascular disease and development of aortic stenosis in relation to HoFH, starting in early childhood.[6, 11] Early detection and intervention are important to attenuate atherogenesis and improve life expectancy.

Heterozygous familial hypercholesterolemia (HeFH)

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.[12] Most HeFH patients remain undiagnosed, which is a problem since their LDL-C levels can be elevated from birth and may reach 7.5-12 mmol/L (290-464 mg/dL).[13]

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, pro-inflammatory 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.[14-18] 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 pro-atherogenic 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 ten subtypes or segments (numbered 1–10), of which subtype 2 two 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.[19] 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 (RR: 1.9, 95%CI: 1.2-2.9), and other studies have added evidence supporting the association.[20] Data of genetic studies are consistent with a causal association between elevated Lp(a) mass levels and increased risk of myocardial infarction and coronary artery disease.[19]

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.[21] The ACC/AHA guidelines do not specify a Lp(a) treatment goal.[22] However, the National Lipid Association reports Lp(a) mass >50 mg/dL (protein; isoform insensitive assay) as a high-risk biomarker.[23]

Clinical effects of lipoprotein apheresis

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),[24] although recent data suggests that the negative impact of LA on QoL is similar to that of haemodialysis.[25] Owing to its invasive nature and ethical concerns, no randomized clinical trials (RCTs) 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.[26]

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.[27] Clinical evidence also suggests that long-term LA contributes to plaque regression and/or stabilization, as well as improvements in prognosis.[27, 28]

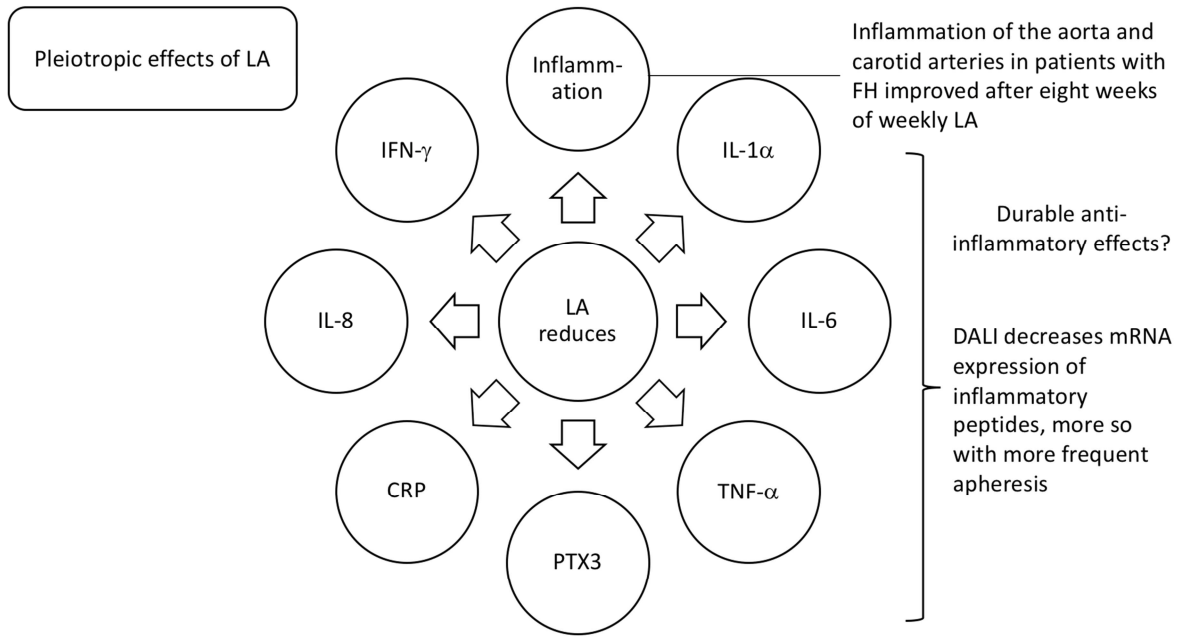
In HoFH, profound lowering of LDL by LA appears to improve coronary atherosclerosis and aortic valvular disease and increase longevity, particularly when treatment is initiated at an early age.[29] Initiation of LA in very young, physically light children can be problematic, but is routinely achieved by skilled medical teams.

Regarding QoL, the considerations for LA are complex. Although LA has the potential to prolong life,[30] 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.[31]

Pleiotropic effects of lipoprotein apheresis

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 (Figure 2).[32]

Figure 2. Lipoprotein apheresis offers more benefits than lowering of lipid levels



Legend: Pleiotropic effects of lipoprotein apheresis (LA).[32-34] 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, interleukin-α; PTX3, pentraxin-3; TNF-α, tumor necrosis factor-α.

Activation of complement in response to LA has been described, as well as reduction of high-sensitivity C-reactive protein (hs-CRP) – a marker of inflammation. Other anti-inflammatory effects

include a reduction of oxidized LDL, P-selectin and ICAM-1.[35, 36] Moreover, a significant reduction of arterial inflammation has been observed after LA in patients with FH.[34, 37]

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 following LA therapy. Blood/plasma viscosity and red blood cell aggregation/deformability are improved with LA.[38] Significant downregulation of mRNA encoding the endothelial damage marker pentraxin-3 (*PTX3*) was seen after the first LA session, while soluble plasma PTX3 levels did not change, but hs-CRP levels did.[39]

Recently, it was demonstrated that LA therapy also removes proprotein convertase subtilisin/kexin type 9 (PCSK9) in patients with severe FH.[36, 40] This was confirmed in a study of 40 patients, and the effect was found to extend to a range of LA types.[36] Both mature and furin-cleaved forms of PCSK9 are removed by LA.[41] Lower PCSK9 levels are associated with lower LDL-C levels.

Lipoprotein apheresis 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 prior to 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 (VLDL), LDL and Lp(a) (but not HDL in general, but possibly specific forms of it[42, 43]) via electrostatic interaction. The heparin extracorporeal LDL precipitation (HELP) system precipitates LDL and Lp(a) at low pH. The precipitate is subsequently removed by filtration**.** Utilizing cascade filtration (CF) or double filtration plasmapheresis (DFPP), plasma components can be removed by using filters with different pore diameters. Large apoB100-containing lipoproteins are removed, while 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 poly-acrylate-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.[26, 35, 44-46]

Non-selective methods

If selective apheresis facilities are not available, non-selective 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.[44]

Whom to treat with lipoprotein apheresis

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 (FCS), or hypertriglyceridemia with pancreatitis.

Guidelines[1] and local institutional clinical protocols[27, 47] 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[27] recommends first reaching a genetic and molecular diagnosis (DNA, skin biopsy to enable determiniation 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 non-invasive and invasive cardiovascular techniques, corneal arcus can indicate the presence of atherosclerosis.[6] Achilles' tendon width has also been found to correlate with calcific atherosclerosis.[48] 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 (MRI) of the coronary arteries and aortic valve. CT and MRI do not exclude catheterization when the treament 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 cardio-, cerebro- and peripheral vascular examinations are strongly recommended. CT angiography (CTA) is the subject of a registry of FH patients, and a recent report has called for CTA to be included in clinical trials of interventions in FH to assist in the development of individualized treatment strategies.[49]

Recent data have been published on pregnant women undergoing LA during pregnancy.[50] 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.[50] 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.

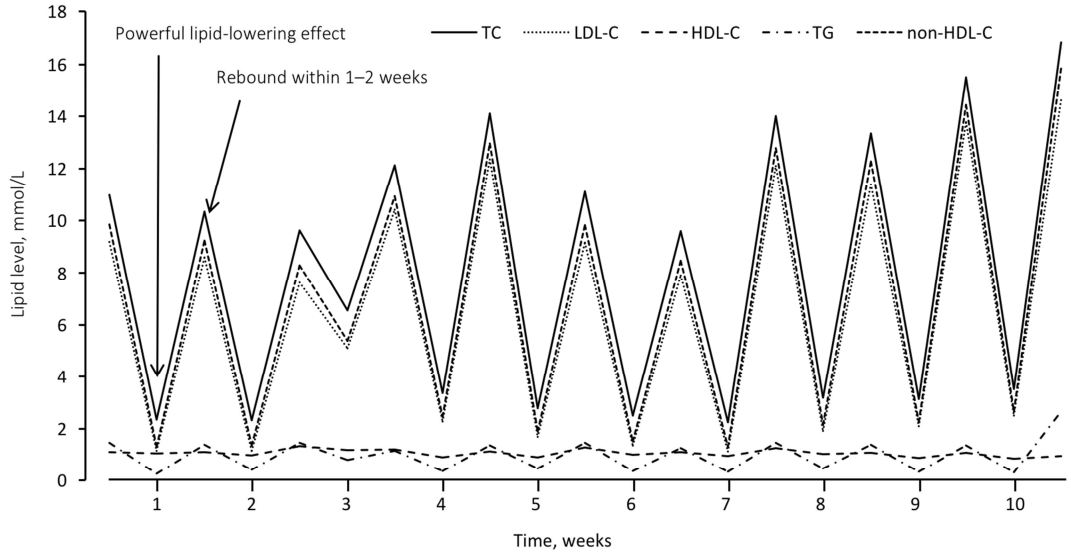
Clinical experience and side effects

Like any therapy, LA can have adverse effects. The most common side effects are mild-to-severe hypotension and nausea.[51-53] Venous access problems can also occur. In a review of over 4000 LA procedures (IMA, DSA and DALI systems), LA was found to be effective and safe for long-term use.[54] Generally, side effects can be managed well by an expert team. Still, in a minority of patients they can be debilitating.[3, 26] Long-term side effects may be more frequent using PEX as opposed to LA.[55]

Cyclical rebound effect between apheresis sessions

An inherent drawback of the method is that LDL-C levels undergo a cyclical rebound effect within 1-2 weeks, between apheresis procedures (Figure 3).[56] In CAD patients treated with atorvastatin, enrolled in the Treating to New Targets (TNT) 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).[57] The ideal frequency of LA is once weekly.

Figure 3. Lipid levels undergo cyclical rebound between apheresis procedures

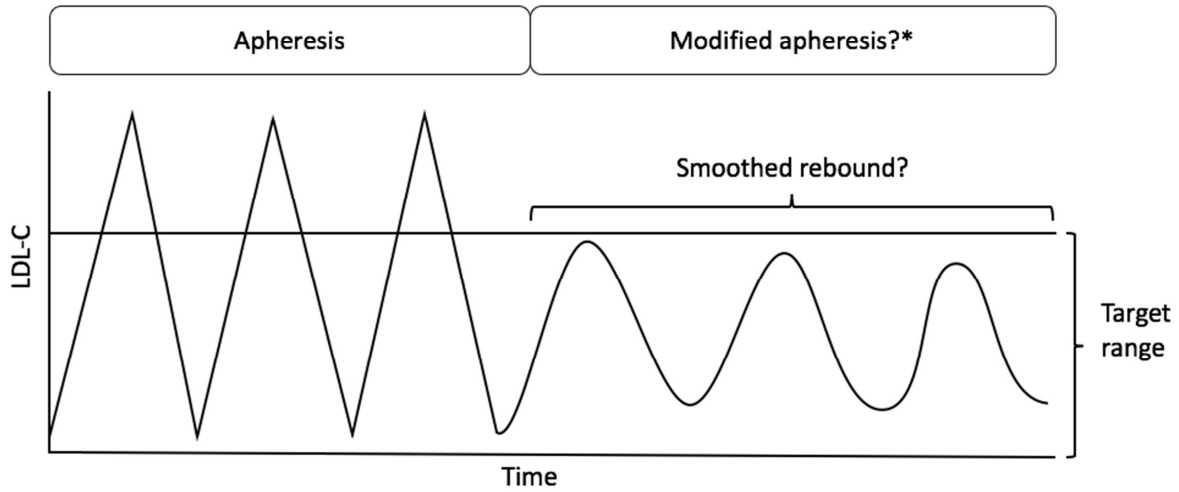


Legend: Representative patient case. HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides.

Attempts should be made to smoothen out the rebound effect between treatments (Figure 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: $C_{mean}=C_{min}+0.73(C_{max}–C_{min})xC_{min,}$ (a coefficient of 0.64 is also frequently used) (Figure 5).[56] Considering the mean interval LDL-C reveals the true extent of the dramatic LDL-C reductions achievable with LA.[56] The utility of mean interval LDL-C values have not been explored extensively in Lp(a).

Figure 4. Improving apheresis outcomes

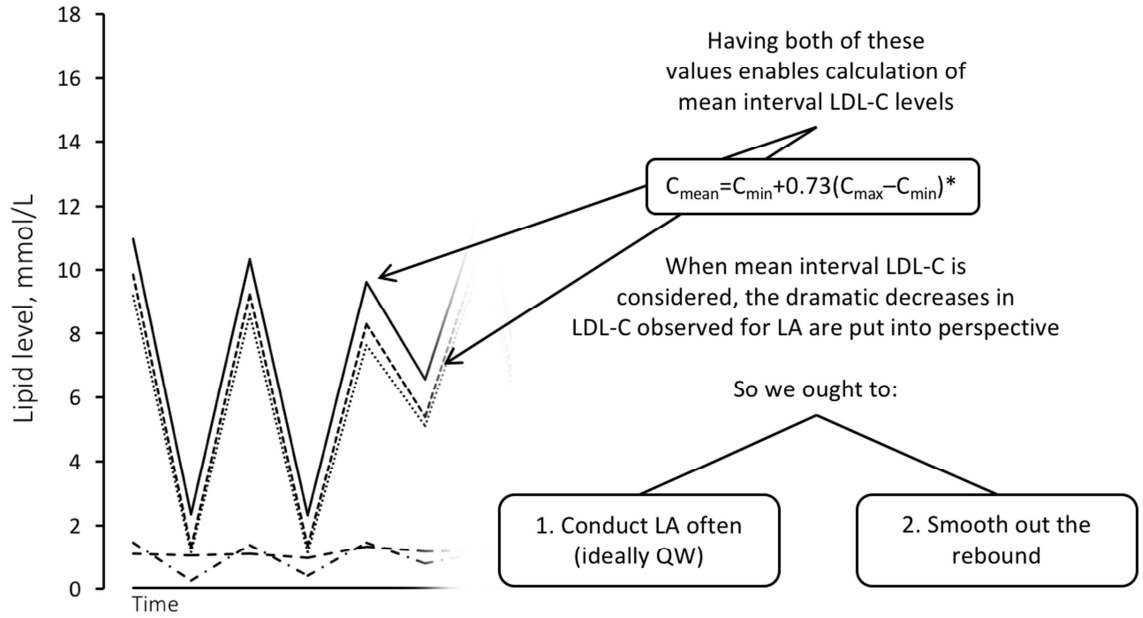
Figure 4. Can we improve outcomes of apheresis?



Legend: 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



Legend: Mean interval LDL-C calculation[56] based on representative patient case; *Coefficient of 0.64 is also used. LA, lipoprotein apheresis; LDL-C, low-density lipoprotein cholesterol; QW, once weekly.

Combining lipoprotein apheresis 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 below) may help to attenuate LDL-C rebound between LA sessions.[58] 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 in order 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.[59] In less severe clinical disease, combination therapy may allow stopping LA altogether, and thus, in some patients, indications may need reconsideration.

Novel treatment options

MTP inhibition

Inhibition of microsomal triglyceride transfer protein (MTP) prevents formation of VLDL in the liver, and chylomicrons in the intestine. MTP normally transfers TGs 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,[60] which was sustained out to 126 weeks.[61] 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 (GI) problems (21% of patients). Increased aminotransferase levels >3x upper limit of normal (34% of patients) and liver fat accumulation >5.56% (78% of patients) have been reported with lomitapide.[60, 62, 63]

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. Since 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 re-challenge 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 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.[64-68] In HeFH patients, decreases in LDL-C were of the order of 40–50%, 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 two null LDLR genes.[69] 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.[64, 66-68]

A 'small interfering RNA' agent is directed against PCSK9 messenger RNA (inclirisan; investigational compound) is in phase 2 development. Results suggest that the drug can reduce LDL-C levels by 28–53% over 180 days.[70]

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.[71] Common adverse events include injection site reactions (76%) and flu-like symptoms (29%), nausea (18%), headache, 15%) and chest pain (12%).[71] 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.[72] These agents remain investigational at present.

Available evidence on integrating lipoprotein apheresis 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.

Homozygous familial hypercholesterolemia (HoFH) – therapeutic options

The latest European Atherosclerosis Society (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.[73] These targets are very seldom met with currently available pharmacological therapy. Different criteria have been formulated in different countries on when LA is indicated in HoFH. The American Society for Apheresis (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.[58] 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.[24] Even lower LDL-C levels may be needed to prevent atherosclerotic disease in older patients.

Apheresis combined with PCSK9 inhibitors. An analysis of the TAUSSIG study of long-term use of evolocumab in patients with HoFH compared the efficacy of the drug with and without apheresis.[65] One hundred and six patients were included in the analysis. All patients were >12 years of age and on stable LDL-lowering therapy. Mean reductions in LDL-C in patients on apheresis were –20.6% at Week 12 (p=0.0012 compared with baseline), and – 23.2 at Week 48 (p=0.0032). There were no differences between LDL-C reductions between patients receiving apheresis at study entry (n=34), and those who were no (n=72) (p=0.38 at Week 12 and p=0.09 at Week 48).[65]

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), three patients permanently discontinued apheresis based on their LDL-C response, and in three patients the time interval between sessions was increased.[60] A post-hoc analysis on data of this study, examined how concomitant apheresis affected the lipid-lowering efficacy of lomitapide.[74] Thirteen of 23 patients who completed the

efficacy phase received LA or conventional therapeutic plasmapheresis (TPE). Concomitant apheresis did not affect LDL reduction (−48% on apheresis, and −55.1% not receiving apheresis, P=0.545).

A recent article reports on seven HoFH patients who were treated with lomitapide in the normal course of their LA therapy (weekly or biweekly), plus statins and ezetimibe.[59] Lomitapide was uptitrated in individual patients, guided by LDL-lowering effects and adverse events. These observations suggest that when patients are receiving non-maximal 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 three patients. In three others, the LDL-C rebound appeared blunted by addition of lomitapide (Figure 6). GI adverse events were manageable.[59]

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.[72] In the first hour following CER-001 infusion, apoA-1 levels increased by 13%. No significant changes in TC, HDL-C and LDL-C were seen, while TG 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%, IQR: −4.4 to −0.62, P=0.012) and a tendency to reduced mean vessel wall thickness (−1.8%, IQR: −3.8 to 0.2%, P=0.081).[72] HDL mimetics remain investigational.

Heterozygous familial hypercholesterolemia (HeFH) – therapeutic options

Statins form the cornerstone of therapy of HeFH patients.[22, 23] 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, 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.[51]

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.[75] 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 1–6. 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.[75] These results show that PCSK9 inhibitors have the potential to significantly reduce or even eradicate the need for apheresis in HeFH patients;[76] 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 25-30%, but the CVD benefit is unknown.[19, 77] 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 (≤125nmol/L).[78] 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.[79]

LA can effectively lower Lp(a) levels. For instance, various apheresis techniques (DALI, DSA, HELP, cascade filtration 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.[26]
LA removes Lp(a) and LDL simultaneously, which makes it hard to distinguish the effects of Lp(a) and LDL-C lowering.[19] 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 (MACE) despite effective LDL-C-lowering treatment.[80, 81] Subsequently adding LA, lowered Lp(a) mass by 73% and the rate of MACE 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.[80] These data have been reviewed in the context of the German national guidelines for LA use.[82]

Specific Lp(a) apheresis using POCARD's Lipopak® immunoadsorption 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.[83]

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

General recommendations: the unmet need for an international registry on lipoprotein apheresis

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 (GLAR),[84] which documents LA treatment procedures, including treatment efficiency, biocompatibility, and clinical safety. After GLAR had been running for two years, 96 German centers had access to the registry, 49 centers were active members, and data of over 700 patients had been entered.[85]

Other registries devoted to therapeutic hemapheresis, but not specifically focusing on LA, include the World Apheresis Association (WAA) Apheresis Registry, a registry that captures various kinds of therapeutic apheresis procedures, including collection or removal of blood corpuscles,[86] 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.[87, 88] Evidence-based guidelines are periodically released by the American Society for Apheresis (ASFA).[1]

An international registry devoted to LA can accumulate data on rare patients who are being treated with non-standard 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 RCTs 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 [ISFA], American Society for Apheresis [ASFA], World Apheresis Association [WAA]), and other scientific societies focused on these arguments such as the International Atherosclerosis Society (IAS), National Lipid Association (NLA) and Lipid-Liga, Italian

Society of Nephrology (SIN), Italian Society of Hemapheresis (SidEM), and facilitate multicenter scientific collaborations on genetic, mechanistic and pooled case studies.

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Conflicts of interests

CS has received honoraria for consultancy and speaking engagements from Aegerion, Fresenius Medical Care and Kaneka NV and research grants from Amgen, MSD, Regeneron, Sanofi, Ionis.
GDS has no conflicts to declare.
GFW received honoraria and research grants from Amgen, Sanofi, Regeneron, Pfizer.
HS has received research grants from Synageva, Pfizer, Amgen, MSD, Genzyme-Sanofi, and has received honoraria and educational grants from AstraZeneca, Aegerion, Amgen, Janssen Cilag Ltd, Lilly, MSD, Pfizer, Sanofi and Synageva.
JVRL has received honoraria for consultancy and speaking engagements from Aegerion and Sanofi.
KW has no conflicts to declare.
LP has received honoraria for consultancy from Chiesi and Amgen and speaking engagements from Sanofi, MSD, Alexion and Mylan
MC has no conflicts to declare.
MHS has received honoraria for consultancy and speaking engagements from Aegerion, Astellas-Amgen, Astellas, Kaneka Medics, Kowa, MSD, Pfizer, Sanofi, Boeringer-ingelheim, AstraZeneca and Daiichi-Sankyo, and research funding from Kaneka Medics, Astellas and Astellas-Amgen.
PM has received honoraria for consultancy and speaking engagements from Genyme, Regeneron, Sanofi-Aventis, Kowa, Pfizer, Amgen, Duke CRI, Eliaz Therapeutics, Aegerion, Ionis, Catabasis, Esperion and Lilly.
UJ has received travel expenses by Aegerion, Diamed, Fresenius Medical Care, Kaneka; honoraria from Aegerion, Amgen, Chiesi, Sanofi, Kaneka, Diamed, Fresenius Medical Care
HK has no conflicts to declare.
VS has conducted held lectures for Amgen GmbH, B.Braun Avitum AG, DIAMED Medizintechnik GmbH, Fresenius Medical Care AG & Co. KGaA, Genzyme GmbH, Kaneka Pharma Europe N.V. German Branch, KWHC Health Consulting GmbH, MSD SHARP & DOHME GMBH, Novartis Pharma GmbH, Pfizer Consumer Healthcare GmbH and Sanofi-Aventis GmbH.

Contributions

All authors made substantial contributions to the drafting of the manuscript, and all reviewed and approved the final draft for submission. There is no original data interpretation in this paper.

Appendix 1. Evidence grading according to the Writing Committee of the American Society for Apheresis[1]

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. *Example: plasma exchange in Guillain-Barre syndrome as 1st-line stand-alone therapy; plasma exchange in myasthenia gravis as 1st-line in conjunction with immunosuppression and cholinesterase inhibition*
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. *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*
III	Optimum role of apheresis therapy is not established. Decision making should be individualized. *Example: extracorporeal photopheresis for nephrogenic systemic fibrosis; plasma exchange in patients with sepsis and multi-organ failure*
IV	Disorders in which published evidence demonstrates or suggests apheresis to be ineffective or harmful. IRB approval is desirable if apheresis treatment is undertaken in these circumstances. *Example: plasma exchange for active rheumatoid arthritis*

Table A2. Grading recommendations

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

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-	Observational studies or case series	Very weak recommendations:

	quality or very low-quality evidence		other alternatives may be equally reasonable

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

*Approved indications vary among countries, †Relative to manufacturers' recommendation for available selective removal devices, §Total number enrolled regardless of treatment assignation; #recent estimates place incidence higher (Sjouke B, et al. Eur Heart J 2015;36:560-5); CR, case report; CS, case series; CT, clinical trial; LDL, low-density lipoprotein; NA, not applicable; RCT, randomized clinical trial; TPE, therapeutic plasma exchange.[89-91]

Appendix 2: Additional members of the Mighty Medic Group*

D'Alessandri G, Immunohematology and Transfusion Medicine, ASL3, Pistoia, Italy; Bianciardi G, Pathological Anatomy, Medical Biotechnology Dept, University of Siena, Italy; Bosco G, Paediatric Cardiology, 'Sapienza' University, 'Umberto I' Hospital, Rome, Italy; De Fusco G, Immunohematology and Transfusion Medicine, "Dell'Angelo" Hospital, Mestre, Italy; Di Giacomo S, Morozzi C, Mesce D, Vitale M, Sovrano B, Extracorporeal Therapy Unit, 'Sapienza' University, Umberto I'Hospital, Rome, Italy; Drogari E, 1st Department of Paediatrics Medical School, "Aghia Sophia" Children's Hospital, Athens, Greece; Ewald N, Internal Medicine Dept, General Hospital Luebbecke-Rahden, Luebbecke, Germany; Gualdi G, Emergency Radiology, 'Sapienza' University, 'Umberto I' Hospital, Rome, Italy; Jaeger BR, Lipid Center Nordrhein, Mu¨lheim an der Ruhr, Germany; Lanti A, Immunohematology and Transfusion Medicine, Tor Vergata University Hospital, Rome, Italy; Marson P, Immunohematology and Transfusion Medicine, General University Hospital, Padua, Italy; Martino F, Paediatric Cardiology, 'Sapienza' University, 'Umberto I' Hospital, Rome, Italy; Migliori G, Immunohematology and Transfusion Medicine, G.B. Morgagni e L. Pierantoni Hospital, Forlì, Italy; Parasassi T, Translational Pharmacology, Science Research Council, Rome, Italy; Pavan A, Immunohematology and Transfusion Medicine, S. Andrea Hospital, Rome, Italy; Perla FM, Paediatric Hemato-Oncology, 'Sapienza' University, 'Umberto I' Hospital, Rome, Italy; Brunelli R, Perrone G, Ginecology and Obstetrics, 'Sapienza' University, 'Umberto I' Hospital, Rome, Italy; Brunelli R, Ginecology and Obstetrics, 'Sapienza' University, 'Umberto I' Hospital, Rome, Italy; Renga S, Nephrology-Dialysis Operative Unit, Giovanni Paolo II Hospital, Olbia, Italy; Ries W, Internal Medicine Dept, Diakonissen Hospital, Flensburg, Germany; Romano N, Immunohematology and Transfusion Medicine, Arcispedale Santa Maria Nuova, Reggio Emilia, Italy; Immunohematology and Transfusion Medicine, General University Hospital, Padua, Italy. Romeo S, Sahlgrenska Academy at University of Gothenburg, Department of Molecular and Clinical Medicine, Gothenburg, Sweden; Pergolini M, Labbadia G, Dept of Internal Medicine and Medical Specialties, 'Sapienza' University, 'Umberto I' Hospital, Rome, Italy; Di Iorio B, Complex Operative Unite Nefrology, Hospital ''A. Landolfi '' Avellino; De Palo T, Operative Unit Pediatric Nephrology and Dialysis, Hospital Giovanni XXIII, Bari; Abbate R, Dept of Medical and Surgical Critical Area, University of Florence; Marcucci R, Dept of Experimental and Clinical Medicine, University of Florence; Poli L, Immunohematology and Transfusion Medicine, Hospital, S. Antonio Abate, Gallarate (MI); Ardissino G, Center for the Treatment and Study of Hemolytic Uremic Syndrome, Foundation IRCCS ''Ca Granda Ospedale Maggiore Policlinico '', Milano; Ottone P, Immunohematology and Transfusion Medicine, Hospital, S.Luigi, Orbassano (TO); Tison T, Immunohematology and Transfusion Medicine, Hospital, Padova; Favari E, Dept of Pharmacy, University of Parma; Borgese L, Shafii M, Gozzer M, Immunohematology and Transfusion Medicine, Sapienza' University, 'Umberto I' Hospital, Rome, Italy; Pacella E, Dept of Sensory Organ, Sapienza' University, 'Umberto I' Hospital, Rome, Italy; Torromeo C, Dept of Cardiovascular Sciences, Respiratory, Nephrology, Anaesthetic and Geriatric, Sapienza' University, 'Umberto I' Hospital, Rome, Italy; Parassassi T, Translational Pharmacology Institute, CNR, Rome; Berni A, Complex Operative Unit, Sapienza' University, S.Andrea Hospital, Rome; Guardamagna O, Pediatric Science Cardiovascular Prevention and Dyslipidemia, Head University of Turin; Zenti M,G, Complex Unit Operative, Endocrinology, Diabetes and Metabolic Diseases, Verona; Guitarrini M,R, Immunohematology and Transfusion Medicine Belcolle Hospital, Viterbo; Berretti D, Operative Unite, Immunohematology of Pistoia; Hohenstein B, FA for internal medicine and nephrology, University Hospital Carl Gustav Carus, Dresda, Germany; Saheb S, Endocrinologie et metabolism, Hospital, Pitiè, Salpètrière, Parigi;

Bjelakovic B, Clinic of Pediatrics, Dept of Cardiology, University of Nis, Serbia; Williams H, Westmead Hospital, Australia; De Luca N, Respiratory Pathophysiology Unit, Dept Internal Medicine and Molecular Specialties, Sapienza University of Rome, Rome, Italy.

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

References

1. Schwartz J, Padmanabhan A, Aqui N, Balogun RA, Connelly-Smith L, Delaney M, Dunbar NM, Witt V, Wu Y and Shaz BH. 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;31:149-62. DOI: 10.1002/jca.21470.
2. Watts GF, Gidding S, Wierzbicki AS, Toth PP, Alonso R, Brown WV, Bruckert E, Defesche J, Lin KK, Livingston M, Mata P, Parhofer KG, Raal FJ, Santos RD, Sijbrands EJ, Simpson WG, Sullivan DR, Susekov AV, Tomlinson B, Wiegman A, Yamashita S and Kastelein JJ. Integrated guidance on the care of familial hypercholesterolaemia from the International FH Foundation. Int J Cardiol. 2014;171:309-25. DOI: 10.1016/j.ijcard.2013.11.025.
3. Cuchel M, Bruckert E, Ginsberg HN, Raal FJ, Santos RD, Hegele RA, Kuivenhoven JA, Nordestgaard BG, Descamps OS, Steinhagen-Thiessen E, Tybjaerg-Hansen A, Watts GF, Averna M, Boileau C, Boren J, Catapano AL, Defesche JC, Hovingh GK, Humphries SE, Kovanen PT, Masana L, Pajukanta P, Parhofer KG, Ray KK, Stalenhoef AF, Stroes E, Taskinen MR, Wiegman A, Wiklund O, Chapman MJ and 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;35:2146-57. DOI: 10.1093/eurheartj/ehu274.
4. Stefanutti C, Morozzi C, Di Giacomo S, Sovrano B, Mesce D and 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;10:782-9. DOI: 10.1016/j.jacl.2016.02.009.
5. Wang A, Richhariya A, Gandra SR, Calimlim B, Kim L, Quek RG, Nordyke RJ and Toth PP. Systematic Review of Low-Density Lipoprotein Cholesterol Apheresis for the Treatment of Familial Hypercholesterolemia. J Am Heart Assoc. 2016;5. DOI: 10.1161/JAHA.116.003294.
6. Cuchel M, Bruckert E, Ginsberg HN, Raal FJ, Santos RD, Hegele RA, Kuivenhoven JA, Nordestgaard BG, Descamps OS, Steinhagen-Thiessen E, Tybjaerg-Hansen A, Watts GF, Averna M, Boileau C, Boren J, Catapano AL, Defesche JC, Hovingh GK, Humphries SE, Kovanen PT, Masana L, Pajukanta P, Parhofer KG, Ray KK, Stalenhoef AF, Stroes E, Taskinen MR, Wiegman A, Wiklund O, Chapman MJ and European Atherosclerosis Society Consensus Panel on Familial Hypercholesterolaemia. 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;35:2146-57. DOI: 10.1093/eurheartj/ehu274.
7. France M, Rees A, Datta B, Thompson G, Capps N, Ferns G, Ramaswami U, Seed M, Neely D, Cramb R, Shoulders C, Barbir M, Pottle A, Eatough R, martin S, Bayly G, Simpson B, Halcox J, Edwards R, Main L, Payn J and Soran H. HEART UK statement on the management of homozygous familial hypercholesterolaemia in the United Kingdom. Atherosclerosis. 2016:In press. DOI: http://dx.doi.org/10.1016/j.atherosclerosis.2016.10.017.
8. Santos RD, Gidding SS, Hegele RA, Cuchel MA, Barter PJ, Watts GF, Baum SJ, Catapano AL, Chapman MJ, Defesche JC, Folco E, Freiberger T, Genest J, Hovingh GK, Harada-Shiba M, Humphries SE, Jackson AS, Mata P, Moriarty PM, Raal FJ, Al-Rasadi K, Ray KK, Reiner Z, Sijbrands EJ, Yamashita S and 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;4:850-61. DOI: 10.1016/S2213-8587(16)30041-9.

9. Zech LA, Jr. and Hoeg JM. Correlating corneal arcus with atherosclerosis in familial hypercholesterolemia. Lipids Health Dis. 2008;7:7. DOI: 10.1186/1476-511X-7-7.
10. Sjouke B, Hovingh GK, Kastelein JJ and Stefanutti C. Homozygous autosomal dominant hypercholesterolemia: prevalence, diagnosis, and current and future treatment perspectives. Curr Opin Lipidol. 2015. DOI: 10.1097/MOL.0000000000000179.
11. Gautschi M, Pavlovic M and Nuoffer JM. Fatal myocardial infarction at 4.5 years in a case of homozygous familial hypercholesterolaemia. JIMD Rep. 2012;2:45-50. DOI: 10.1007/8904_2011_45.
12. Huijgen R, Hutten BA, Kindt I, Vissers MN and 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;5:354-9. DOI: 10.1161/CIRCGENETICS.111.962456.
13. Marshall WJ, Bangert SK and Lapsley M. *Clinical Chemistry*. St. Louis, MO: Mosby; 2012.
14. Boffa MB and Koschinsky ML. Screening for and management of elevated Lp(a). Curr Cardiol Rep. 2013;15:417. DOI: 10.1007/s11886-013-0417-8.
15. Brown WV, Moriarty PM, Remaley AT and Tsimikas S. JCL Roundtable: Should we treat elevations in Lp(a)? J Clin Lipidol. 2016;10:215-24. DOI: 10.1016/j.jacl.2016.02.012.
16. Koschinsky ML. Novel insights into Lp(a) physiology and pathogenicity: more questions than answers? Cardiovasc Hematol Disord Drug Targets. 2006;6:267-78.
17. Marcovina SM and 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;2:335-44. DOI: 10.1055/s-2002-35404.
18. Yeang C, Witztum JL and 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;26:169-78. DOI: 10.1097/MOL.0000000000000171.
19. Kronenberg F and Utermann G. Lipoprotein(a): resurrected by genetics. J Intern Med. 2013;273:6-30. DOI: 10.1111/j.1365-2796.2012.02592.x.
20. Qin SY, Liu J, Jiang HX, Hu BL, Zhou Y and Olkkonen VM. Association between baseline lipoprotein (a) levels and restenosis after coronary stenting: meta-analysis of 9 cohort studies. Atherosclerosis. 2013;227:360-6. DOI: 10.1016/j.atherosclerosis.2013.01.014.
21. Nordestgaard BG, Chapman MJ, Ray K, Boren J, Andreotti F, Watts GF, Ginsberg H, Amarenco P, Catapano A, Descamps OS, Fisher E, Kovanen PT, Kuivenhoven JA, Lesnik P, Masana L, Reiner Z, Taskinen MR, Tokgozoglu L, Tybjaerg-Hansen A and European Atherosclerosis Society Consensus P. Lipoprotein(a) as a cardiovascular risk factor: current status. Eur Heart J. 2010;31:2844-53. DOI: 10.1093/eurheartj/ehq386.
22. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, Goldberg AC, Gordon D, Levy D, Lloyd-Jones DM, McBride P, Schwartz JS, Shero ST, Smith SC, Jr., Watson K, Wilson PW, Eddleman KM, Jarrett NM, LaBresh K, Nevo L, Wnek J, Anderson JL, Halperin JL, Albert NM, Bozkurt B, Brindis RG, Curtis LH, DeMets D, Hochman JS, Kovacs RJ, Ohman EM, Pressler SJ, Sellke FW, Shen WK, Smith SC, Jr., Tomaselli GF and 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:S1-45. DOI: 10.1161/01.cir.0000437738.63853.7a.

23. Jacobson TA, Ito MK, Maki KC, Orringer CE, Bays HE, Jones PH, McKenney JM, Grundy SM, Gill EA, Wild RA, Wilson DP and Brown WV. National Lipid Association recommendations for patient-centered management of dyslipidemia: part 1 - executive summary. J Clin Lipidol. 2014;8:473-88. DOI: 10.1016/j.jacl.2014.07.007.
24. Graesdal A, Bogsrud MP, Holven KB, Nenseter MS, Narverud I, Langslet G, Brekke M, Retterstol K, Arnesen KE and Ose L. Apheresis in homozygous familial hypercholesterolemia: the results of a follow-up of all Norwegian patients with homozygous familial hypercholesterolemia. J Clin Lipidol. 2012;6:331-9. DOI: 10.1016/j.jacl.2012.03.004.
25. Stasiewski E, Christoph M, Christoph A, Bittner A, Weidner K and 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;18:233-40. DOI: 10.1016/j.atherosclerosissup.2015.02.035.
26. Stefanutti C, Morozzi C, Di Giacomo S and 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;17:169-78. DOI: 10.1111/j.1744-9987.2012.01142.x.
27. Stefanutti C, Vivenzio A, Di Giacomo S, Mazzarella B, Bosco G and Berni A. Aorta and coronary angiographic follow-up of children with severe hypercholesterolemia treated with low-density lipoprotein apheresis. Transfusion. 2009;49:1461-70. DOI: 10.1111/j.1537-2995.2009.02135.x.
28. Schuff-Werner P, Fenger S and Kohlschein P. Role of lipid apheresis in changing times. Clin Res Cardiol Suppl. 2012;7:7-14. DOI: 10.1007/s11789-012-0049-3.
29. Thompson GR. The evidence-base for the efficacy of lipoprotein apheresis in combating cardiovascular disease. Atheroscler Suppl. 2013;14:67-70. DOI: 10.1016/j.atherosclerosissup.2012.10.001.
30. Thompson GR, Miller JP and Breslow JL. Improved survival of patients with homozygous familial hypercholesterolaemia treated with plasma exchange. Br Med J (Clin Res Ed). 1985;291:1671-3.
31. Bruckert E, Saheb S, Bonté JR and Coudray-Omnès C. Daily life, experience and needs of persons suffering from homozygous familial hypercholesterolaemia: insights from a patient survey. Atherosclerosis Supplements. 2014;15:46-51.
32. Stefanutti C, Vivenzio A, Di Giacomo S and Ferraro PM. Cytokines profile in serum of homozygous familial hypercholesterolemia is changed by LDL-apheresis. Cytokine. 2011;55:245-50. DOI: 10.1016/j.cyto.2011.04.003.
33. Hovland A, Hardersen R, Sexton J, Mollnes TE and Lappegard KT. Different inflammatory responses induced by three LDL-lowering apheresis columns. J Clin Apher. 2009;24:247-53. DOI: 10.1002/jca.20223.
34. van Wijk DF, Sjouke B, Figueroa A, Emami H, van der Valk FM, MacNabb MH, Hemphill LC, Schulte DM, Koopman MG, Lobatto ME, Verberne HJ, Fayad ZA, Kastelein JJ, Mulder WJ, Hovingh GK, Tawakol A and Stroes ES. Nonpharmacological lipoprotein apheresis reduces arterial inflammation in familial hypercholesterolemia. J Am Coll Cardiol. 2014;64:1418-26. DOI: 10.1016/j.jacc.2014.01.088.
35. Arai K, Orsoni A, Mallat Z, Tedgui A, Witztum JL, Bruckert E, Tselepis AD, Chapman MJ and Tsimikas S. Acute impact of apheresis on oxidized phospholipids in patients with familial hypercholesterolemia. J Lipid Res. 2012;53:1670-8. DOI: 10.1194/jlr.P027235.

36. Julius U, Milton M, Stoellner D, Rader D, Gordon B, Polk D, Waldmann E, Parhofer KG and Moriarty PM. Effects of lipoprotein apheresis on PCSK9 levels. Atheroscler Suppl. 2015;18:180-6. DOI: 10.1016/j.atherosclerosissup.2015.02.028.
37. Schettler V, Methe H, Staschinsky D, Schuff-Werner P, Muller GA and Wieland E. Review: the oxidant/antioxidant balance during regular low density lipoprotein apheresis. Ther Apher. 1999;3:219-26.
38. Moriarty PM and Hemphill L. Lipoprotein apheresis. Cardiol Clin. 2015;33:197-208. DOI: 10.1016/j.ccl.2015.02.002.
39. Stefanutti C, Mazza F, Steiner M, Watts GF, De Neve J, Pasqualetti D and Paal J. 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. DOI: 10.1155/2016/4739512.
40. Tavori H, Giunzioni I, Linton MF and Fazio S. Loss of plasma proprotein convertase subtilisin/kexin 9 (PCSK9) after lipoprotein apheresis. Circ Res. 2013;113:1290-5. DOI: 10.1161/CIRCRESAHA.113.302655.
41. Hori M, Ishihara M, Yuasa Y, Makino H, Yanagi K, Tamanaha T, Kishimoto I, Kujiraoka T, Hattori H and Harada-Shiba M. 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:E41-9. DOI: 10.1210/jc.2014-3066.
42. Moriarty PM, Luyendyk JP, Gibson CA and Backes JM. Effect of low-density lipoprotein apheresis on plasma levels of apolipoprotein e4. Am J Cardiol. 2010;105:1585-7. DOI: 10.1016/j.amjcard.2010.01.018.
43. Opole IO, Belmont JM, Kumar A and Moriarty PM. Effect of low-density lipoprotein apheresis on inflammatory and noninflammatory high-density lipoprotein cholesterol. Am J Cardiol. 2007;100:1416-8. DOI: 10.1016/j.amjcard.2007.06.033.
44. Winters JL. Lipid apheresis, indications, and principles. J Clin Apher. 2011;26:269-75. DOI: 10.1002/jca.20299.
45. Julius U, Fischer S, Schatz U, Hohenstein B and Bornstein S. Lipoprotein aphersis: an update. Clin Lipidol. 2013;8:693-705.
46. Julius U, Fischer S, Schatz U, Passauer J and Bornstein S. Why an apheresis center should offer more than one lipoprotein apheresis method. Ther Apher Dial. 2013;17:179-84. DOI: 10.1111/j.1744-9987.2012.01129.x.
47. Schettler V, Neumann CL, Hulpke-Wette M, Hagenah GC, Schulz EG, Wieland E and German Apheresis Working G. Current view: indications for extracorporeal lipid apheresis treatment. Clin Res Cardiol Suppl. 2012;7:15-9. DOI: 10.1007/s11789-012-0046-6.
48. Raal FJ and Santos RD. Homozygous familial hypercholesterolemia: current perspectives on diagnosis and treatment. Atherosclerosis. 2012;223:262-8. DOI: 10.1016/j.atherosclerosis.2012.02.019.
49. Sijbrands EJ, Nieman K, Budoff MJ and Consortium FC. Cardiac computed tomography imaging in familial hypercholesterolaemia: implications for therapy and clinical trials. Curr Opin Lipidol. 2015;26:586-92. DOI: 10.1097/MOL.0000000000000249.
50. Ogura M, Makino H, Kamiya C, Yoshimatsu J, Soran H, Eatough R, Perrone G, Harada-Shiba M and Stefanutti C. Lipoprotein apheresis is essential for managing pregnancies in patients with

homozygous familial hypercholesterolemia: Seven case series and discussion. Atherosclerosis. 2016. DOI: http://dx.doi.org/10.1016/j.atherosclerosis.2016.10.018.

51. Stefanutti C and Julius U. Lipoprotein apheresis: state of the art and novelties. Atheroscler Suppl. 2013;14:19-27. DOI: 10.1016/j.atherosclerosissup.2012.10.021.
52. Heigl F, Hettich R, Lotz N, Reeg H, Pflederer T, Osterkorn D, Osterkorn K and Klingel R. 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;18:154-62. DOI: 10.1016/j.atherosclerosissup.2015.02.013.
53. Dittrich-Riediger J, Schatz U, Hohenstein B and Julius U. Adverse events of lipoprotein apheresis and immunoadsorption at the Apheresis Center at the University Hospital Dresden. Atheroscler Suppl. 2015;18:45-52. DOI: 10.1016/j.atherosclerosissup.2015.02.007.
54. Bambauer R, Schiel R and Latza R. Low-density lipoprotein apheresis: an overview. Ther Apher Dial. 2003;7:382-90.
55. Health Quality Ontario. Low-density lipoprotein apheresis: an evidence-based analysis. Ont Health Technol Assess Ser. 2007;7:1-101.
56. Kroon AA, van't Hof MA, Demacker PN and Stalenhoef AF. The rebound of lipoproteins after LDL-apheresis. Kinetics and estimation of mean lipoprotein levels. Atherosclerosis. 2000;152:519-26. DOI: 10.1016/S0021-9150(00)00371-3.
57. 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;65:1539-48. DOI: 10.1016/j.jacc.2015.02.017.
58. Stefanutti C and Thompson GR. Lipoprotein apheresis in the management of familial hypercholesterolaemia: historical perspective and recent advances. Curr Atheroscler Rep. 2015;17:465. DOI: 10.1007/s11883-014-0465-6.
59. Stefanutti C, Morozzi C, Di Giacomo S, Sovrano B, Mesce D and Grossi A. Management of homozygous familial hypercholesterolaemia in real-world clinical practice: a report of seven Italian patients treated in Rome with lomitapide and lipoprotein apheresis. J Clin Lipidol. 2016;in press. DOI: 10.1016/j.jacl.2016.02.009.
60. Cuchel M, Meagher EA, du Toit Theron H, Blom DJ, Marais AD, Hegele RA, Averna MR, Sirtori CR, Shah PK, Gaudet D, Stefanutti C, Vigna GB, Du Plessis AM, Propert KJ, Sasiela WJ, Bloedon LT, Rader DJ and 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;381:40-6. DOI: 10.1016/S0140-6736(12)61731-0.
61. Blom DJ, Averna M, Meagher EA, du Toit Theron H, Sirtori CR, Hegele RA, Shah PK, Gaudet D, Stefanutti C, Vigna GB, Foulds P, Bloedon LT, Rader DJ and Cuchel M. Long-term efficacy and safety of lomitapide for the treatment of homozygous familial hypercholesterolemia: results of the Phase 3 extension trial. Paper presented at: AHA; 2015; Orlando, Florida.
62. Aegerion Pharmaceuticals Inc. Lojuxta summary of product characteristics. 2015.
63. Cuchel M, Bloedon LT, Szapary PO, Kolansky DM, Wolfe ML, Sarkis A, Millar JS, Ikewaki K, Siegelman ES, Gregg RE and Rader DJ. Inhibition of microsomal triglyceride transfer protein in familial hypercholesterolemia. N Engl J Med. 2007;356:148-56. DOI: 10.1056/NEJMoa061189.
64. Raal FJ, Honarpour N, Blom DJ, Hovingh GK, Xu F, Scott R, Wasserman SM, Stein EA and Investigators T. Inhibition of PCSK9 with evolocumab in homozygous familial hypercholesterolaemia (TESLA Part B): a randomised, double-blind, placebo-controlled trial. Lancet. 2015;385:341-50. DOI: 10.1016/S0140-6736(14)61374-X.

65. Raal FJ, Hovingh GK, Blom D, Santos RD, Harada-Shiba M, Bruckert E, Couture P, Soran H, Watts GF, Kurtz C, Honarpour N, Tang L, Kasichayanula S, Wasserman SM and Stein EA. 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. DOI: 10.1016/S2213-8587(17)30044-X.
66. Zhang XL, Zhu QQ, Zhu L, Chen JZ, Chen QH, Li GN, Xie J, Kang LN and Xu B. Safety and efficacy of anti-PCSK9 antibodies: a meta-analysis of 25 randomized, controlled trials. BMC Med. 2015;13:123. DOI: 10.1186/s12916-015-0358-8.
67. Robinson JG, Farnier M, Krempf M, Bergeron J, Luc G, Averna M, Stroes ES, Langslet G, Raal FJ, El Shahawy M, Koren MJ, Lepor NE, Lorenzato C, Pordy R, Chaudhari U and Kastelein JJ. Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. N Engl J Med. 2015;372:1489-99. DOI: 10.1056/NEJMoa1501031.
68. Cannon CP, Cariou B, Blom D, McKenney JM, Lorenzato C, Pordy R, Chaudhari U and Colhoun HM. 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;36:1186-94. DOI: 10.1093/eurheartj/ehv028.
69. Stein EA, Honarpour N, Wasserman SM, Xu F, Scott R and Raal FJ. Effect of the proprotein convertase subtilisin/kexin 9 monoclonal antibody, AMG 145, in homozygous familial hypercholesterolemia. Circulation. 2013;128:2113-20. DOI: 10.1161/CIRCULATIONAHA.113.004678.
70. Ray KK, Landmesser U, Leiter LA, Kallend D, Dufour R, Karakas M, Hall T, Troquay RP, Turner T, Visseren FL, Wijngaard P, Wright RS and Kastelein JJ. Inclisiran in Patients at High Cardiovascular Risk with Elevated LDL Cholesterol. N Engl J Med. 2017. DOI: 10.1056/NEJMoa1615758.
71. Raal FJ, Santos RD, Blom DJ, Marais AD, Charng MJ, Cromwell WC, Lachmann RH, Gaudet D, Tan JL, Chasan-Taber S, Tribble DL, Flaim JD and Crooke ST. 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. DOI: 10.1016/S0140-6736(10)60284-X.
72. Hovingh GK, Smits LP, Stefanutti C, Soran H, Kwok S, de Graaf J, Gaudet D, Keyserling CH, Klepp H, Frick J, Paolini JF, Dasseux JL, Kastelein JJ and Stroes ES. 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. DOI: 10.1016/j.ahj.2015.01.008.
73. Catapano AL, Graham I, De Backer G, Wiklund O, Chapman MJ, Drexel H, Hoes AW, Jennings CS, Landmesser U, Pedersen TR, Reiner Z, Riccardi G, Taskinen MR, Tokgozoglu L, Verschuren WM, Vlachopoulos C, Wood DA, Zamorano JL, 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 Assocciation for Cardiovascular Prevention & Rehabilitation (EACPR). Eur Heart J. 2016. DOI: 10.1093/eurheartj/ehw272.
74. Stefanutti C, Blom DJ, Averna MR, Meagher EA, Theron H, Marais AD, Hegele RA, Sirtori CR, Shah PK, Gaudet D, Vigna GB, Sachais BS, Di Giacomo S, du Plessis AM, Bloedon LT, Balser J, Rader DJ, Cuchel M and 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;240:408-14. DOI: 10.1016/j.atherosclerosis.2015.03.014.

75. Moriarty PM, Parhofer KG, Babirak SP, Cornier MA, Duell PB, Hohenstein B, Leebmann J, Ramlow W, Schettler V, Simha V, Steinhagen-Thiessen E, Thompson PD, Vogt A, von Stritzky B, Du Y and Manvelian G. Alirocumab in patients with heterozygous familial hypercholesterolaemia undergoing lipoprotein apheresis: the ODYSSEY ESCAPE trial. Eur Heart J. 2016. DOI: 10.1093/eurheartj/ehw388.
76. Watts GF and Stefanutti C. ODYSSEY ESCAPE: is PCSK9 inhibition the Trojan Horse for the use of lipoprotein apheresis in familial hypercholesterolaemia? Eur Heart J. 2016:In press. DOI: 10.1093/eurheartj/ehw497.
77. Stein EA and Raal F. Future Directions to Establish Lipoprotein(a) as a Treatment for Atherosclerotic Cardiovascular Disease. Cardiovasc Drugs Ther. 2016. DOI: 10.1007/s10557-016-6654-5.
78. Raal FJ, Giugliano RP, Sabatine MS, Koren MJ, Langslet G, Bays H, Blom D, Eriksson M, Dent R, Wasserman SM, Huang F, Xue A, Albizem M, Scott R and Stein EA. Reduction in lipoprotein(a) with PCSK9 monoclonal antibody evolocumab (AMG 145): a pooled analysis of more than 1,300 patients in 4 phase II trials. J Am Coll Cardiol. 2014;63:1278-88. DOI: 10.1016/j.jacc.2014.01.006.
79. Viney NJ, van Capelleveen JC, Geary RS, Xia S, Tami JA, Yu RZ, Marcovina SM, Hughes SG, Graham MJ, Crooke RM, Crooke ST, Witztum JL, Stroes ES and Tsimikas S. Antisense oligonucleotides targeting apolipoprotein(a) in people with raised lipoprotein(a): two randomised, double-blind, placebo-controlled, dose-ranging trials. Lancet. 2016. DOI: 10.1016/S0140-6736(16)31009-1.
80. Jaeger BR, Richter Y, Nagel D, Heigl F, Vogt A, Roeseler E, Parhofer K, Ramlow W, Koch M, Utermann G, Labarrere CA, 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;6:229-39. DOI: 10.1038/ncpcardio1456.
81. Roeseler E, Julius U, Heigl F, Spitthoever R, Heutling D, Breitenberger P, Leebmann J, Lehmacher W, Kamstrup PR, Nordestgaard BG, Maerz W, Noureen A, Schmidt K, Kronenberg F, Heibges A, Klingel R and 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;36:2019-27. DOI: 10.1161/ATVBAHA.116.307983.
82. Klingel R, Heibges A, Fassbender C and 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. DOI: 10.1007/s11789-017-0082-3.
83. Safarova MS, Ezhov MV, Afanasieva OI, Matchin YG, Atanesyan RV, Adamova IY, Utkina EA, Konovalov GA and Pokrovsky SN. Effect of specific lipoprotein(a) apheresis on coronary atherosclerosis regression assessed by quantitative coronary angiography. Atheroscler Suppl. 2013;14:93-9. DOI: 10.1016/j.atherosclerosissup.2012.10.015.
84. Nestruck AC and Davignon J. Risks for hyperlipidemia. Cardiol Clin. 1986;4:47-56.
85. Schettler VJ, Neumann CL, Peter C, Zimmermann T, Julius U, Roeseler E, Heigl F, Ramlow W, Blume H and Scientific Board of GftGAWG. First data from the German Lipoprotein Apheresis Registry (GLAR). Atheroscler Suppl. 2015;18:41-4. DOI: 10.1016/j.atherosclerosissup.2015.02.006.
86. Association WA. New World Apheresis Association Apheresis Registry. 2016.

87. Passalacqua S, Staffolani E, Busnach G, Roccatello D, Pasquali S, Cappelli P, Liuzzo G and 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;20:101-6. DOI: 10.1002/jca.20037.
88. De Silvestro G, Bagatella P, Vicarioto M, Tison T and Marson P. The Italian SIdEM registry for apheresis: an overview of the 2005 statistics. Int J Artif Organs. 2008;31:354-62.
89. Sjouke B, Kusters DM, Kindt I, Besseling J, Defesche JC, Sijbrands EJ, Roeters van Lennep JE, Stalenhoef AF, Wiegman A, de Graaf J, Fouchier SW, Kastelein JJ and Hovingh GK. Homozygous autosomal dominant hypercholesterolaemia in the Netherlands: prevalence, genotype-phenotype relationship, and clinical outcome. Eur Heart J. 2015;36:560-565. DOI: 10.1093/eurheartj/ehu058.
90. Do R, Stitziel NO, Won HH, Jorgensen AB, Duga S, Angelica Merlini P, Kiezun A, Farrall M, Goel A, Zuk O, Guella I, Asselta R, Lange LA, Peloso GM, Auer PL, Project NES, Girelli D, Martinelli N, Farlow DN, DePristo MA, Roberts R, Stewart AF, Saleheen D, Danesh J, Epstein SE, Sivapalaratnam S, Kees Hovingh G, Kastelein JJ, Samani NJ, Schunkert H, Erdmann J, Shah SH, Kraus WE, Davies R, Nikpay M, Johansen CT, Wang J, Hegele RA, Hechter E, Marz W, Kleber ME, Huang J, Johnson AD, Li M, Burke GL, Gross M, Liu Y, Assimes TL, Heiss G, Lange EM, Folsom AR, Taylor HA, Olivieri O, Hamsten A, Clarke R, Reilly DF, Yin W, Rivas MA, Donnelly P, Rossouw JE, Psaty BM, Herrington DM, Wilson JG, Rich SS, Bamshad MJ, Tracy RP, Adrienne Cupples L, Rader DJ, Reilly MP, Spertus JA, Cresci S, Hartiala J, Wilson Tang WH, Hazen SL, Allayee H, Reiner AP, Carlson CS, Kooperberg C, Jackson RD, Boerwinkle E, Lander ES, Schwartz SM, Siscovick DS, McPherson R, Tybjaerg-Hansen A, Abecasis GR, Watkins H, Nickerson DA, Ardissino D, Sunyaev SR, O'Donnell CJ, Altshuler D, Gabriel S and Kathiresan S. Exome sequencing identifies rare LDLR and APOA5 alleles conferring risk for myocardial infarction. Nature. 2015;518:102-106. DOI: 10.1038/nature13917.
91. Benn M, Watts GF, Tybjaerg-Hansen A and Nordestgaard BG. Familial hypercholesterolemia in the Danish general population: prevalence, coronary artery disease, and cholesterol-lowering medication. J Clin Endocrinol Metab. 2012;97:3956-64. DOI: 10.1210/jc.2012-1563.

Highlights

- Lipoprotein apheresis (LA) is a cornerstone of therapy in severe dyslipidemias
- Novel pharmacotherapies are emerging, some of which can be used alongside LA
- We consider the evidence for the appropriate use of LA in these settings