

Mini Review

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Therapeutic Apheresis for Homozygous Familial Hypercholesterolemia Turns 50

Claudia Stefanutti^{1*}

¹Department of Molecular Medicine, Extracorporeal Therapeutic Techniques Unit, Lipid Clinic and Atherosclerosis Prevention Centre, Regional Centre for Rare Diseases, Immunohematology and Transfusion Medicine, Umberto I Hospital, "Sapienza" University of Rome, Viale del Policlinico 155, Rome, 00161, Italy.

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*Correspondence:

*Prof. Dr. Claudia Stefanutti, MD, PhD, Department of Molecular Medicine, Extracorporeal Therapeutic Techniques Unit, Lipid Clinic and Atherosclerosis Prevention Centre, Regional Centre for Rare Diseases, Immunohematology and Transfusion Medicine, Umberto I Hospital, "Sapienza" University of Rome, Viale del Policlinico 155, Rome, 00161, Italy;
Email: claudia.stefanutti@uniroma1.it.

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Abstract

Familial hypercholesterolemia (FH) is a genetic autosomal dominant metabolic disorder that is characterized by elevated plasma and lipoprotein levels, such as low-density lipoprotein cholesterol (LDL-C) that carry atherogenic lipids in plasma. There are two forms of FH: Heterozygous Familial Hypercholesterolemia (HeFH), a relatively frequent genetic disorder affecting roughly 1 in 200–300 people worldwide, causing high LDL-C and early atherosclerotic cardiovascular disease (ASCVD). Homozygous Familial Hypercholesterolemia (HoFH) is a rare, severe form occurring in 1 in 160,000 to 1,000,000 people. Early diagnosis and lifelong treatment are essential for patients with FH to reduce the risk of developing cardiovascular disease early in life, increase life expectancy, and improve quality of life. This mini review offers a targeted historical and clinical review of the 5-decade development of extracorporeal treatment methods, especially Lipoprotein Apheresis (LA), in the treatment of HoFH. Besides the overview of its proven efficacy, safety, and pleiotropic activity, the review briefly describes the modern role of LA and new lipid-lowering treatments and their role in the remaining patient groups.

Literature Search Strategy

This mini review aimed to provide a narrow historical and clinical overview of the 5-decade development of therapeutic apheresis in homozygous familial hypercholesterolemia (HoFH). A specific search of PubMed, Scopus, and Google Scholar was conducted using keywords such as *HoFH*, *Lipoprotein Apheresis*, *LDL apheresis*, *plasmapheresis*, and *therapeutic apheresis*. The emphasis was on historical reports, significant clinical trials, and new international guidelines relevant to the modern role of LA.

Mini Review

The year 2025 marks the 50th anniversary of the landmark report published in *The Lancet*, with Gilbert R Thompson as first author († January 9, 2026): '*Plasma exchange in the management of Homozygous Familial Hypercholesterolaemia (HoFH)*'. G R Thompson, R Lowenthal, N B Myant. *Lancet*. 1975 May 31;1(7918):1208-11. Thompson et al submitted to the plasma-exchange (PEX) two young women with HoFH and coronary and aortic atheromas. The patients underwent repeated plasma-exchange procedures, using a continuous-flow blood-cell separator, for 4 and 8 months. A pronounced reduction in plasma cholesterol and LDL-C levels was achieved. Side effects were not observed, and both patients' angina symptoms disappeared. Thompson concluded that PEX was a novel and practical approach to the long-term management of HoFH, rightly defined as a lethal disorder. The extracorporeal treatment induced

mitigation and suppression of angina symptoms providing possible information about the possible reversibility of human atheroma. Two years later, Lupien et al confirmed the potential of this innovative approach by introducing a technical variant that enabled the selective removal of LDL in two HeFH patients and a normocholesterolemic volunteer. This pioneering technique would later be called LDL-apheresis (LDL-a). LDL-a demonstrated several advantages over PEX, the most significant, from a metabolic standpoint, being the avoidance of a reduction in plasma HDL-cholesterol levels, which is known to be inversely correlated with ASCVD risk, and non-significant depletion of other plasma proteins: albumin and immunoglobulins. Other investigators subsequently introduced several technical refinements of LDL-apheresis, now collectively defined as Lipoprotein Apheresis (LA). As summarized in Table 1, this technological evolution—from plasma exchange to increasingly selective adsorption and filtration systems—substantially improved treatment specificity, procedural safety, and long-term clinical applicability in patients with severe familial hypercholesterolemia. Determinants of efficacy are the acute reduction in lipids and lipoproteins achieved by each apheresis procedure, their frequency (interval between treatments), and the fractional catabolic rates and hepatic pool sizes of LDL or lipoprotein (a) [Lp(a)] of the patient being treated. Calculated estimate of the efficacy of apheresis is the decrease in the interval (time-averaged) mean of serum total or LDL-C or Lp(a), between procedures, expressed as the percent decrease in the interval means below the maximal levels of these lipoproteins after all treatment. Nowadays, LA represents the ‘standard of care’ for HoFH patients to acutely reduce LDL-C up to 50-60%. Patients are submitted to extracorporeal procedures every 7-15 days. Combining LA with usual and novel lipid-lowering drugs is recommended as a novel therapeutic approach to obtain a further LDL-C reduction, smoothing LDL-C ‘rebound’, after LA. At present, LA retains several important clinical indications. In our opinion, the most important are: treatment of pediatric HoFH patients, pregnant HoFH women, and Lp(a)-lowering in isolated and severe forms of

Table 1. Technological and conceptual evolution of lipid therapeutic apheresis in the treatment of Familial Hypercholesterolemia – Heterozygous and Homozygous forms.

Year	Author	Technique
1967	De Gennes JL	Discontinuous flow apheresis
1972	Turnberg LA	Plasma-Exchange
1975	Thompson GR	Plasma-Exchange
1981	Hayashi R	Cascade Filtration
1981	Kikkeva T	Cascade Filtration
1983	Baeyer H	Cascade Filtration
1984-5	Yokoyama S	Double adsorption
1986	Seidel S	Double Precipitation with Heparin
1987	Antwiter GD	Double adsorption with Dextran

Table 2. Children with HoFH treated with LA

Courtesy of Prof. GR Thompson

Children with homozygous FH who started on lipoprotein apheresis before age 5

Source	Age yrs	LDL-C mmol/l	Method *	Frequency days	Duration month/yr
Stefanutti (1997)	4.5	19.4	DSA	15	1.5 m
Stefanutti (2001)	3.5	24.3	DSA	15	4.5 m
Hudgins (2008)	3	18.4	DSA	14	32 m
Palcoux (2008)	3.5	23.0	DSA/ DALI	14	7.7 y
	4.8	19.2	" "	14	21 y
Lefort (2009)	4.5	24.9	DALI	14	12 m
Coker (2009)	4	20.9	DFPP/ APP	14	22 m
	2	18.3	" "	14	58 m
Mann (2013)	2.25	23.2	PP/ DSA	7	72 m
Mean	3.6	21.3		13	1.5 m- 21 y

*DSA, dextran sulphate adsorption; DALI, direct adsorption of lipoproteins; DFPP, double filtration plasmapheresis; APP, adsorption plasmapheresis; PP, plasmapheresis

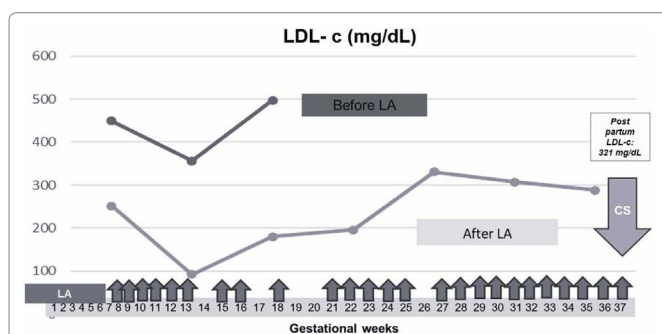


Figure 1. LDL-C before and after LA in HoFH pregnancy. LDL-C: LDL cholesterol; LA: lipoprotein apheresis; HoFH: homozygous familial hypercholesterolemia; CS: cesarean section. (*)

(*): Ref # 15. Stefanutti C, et al. Management of a young HoFH patient during pregnancy using Lipoprotein Apheresis (whole blood): A novel experience. Transfus Apher Sci. 2025 Feb;64(1):104062.

Hyperlipidemia associated with progressive ASCVD [table 2, figure 1].

Over the last few years, the therapeutic landscape of HoFH has changed significantly with the introduction of PCSK9 inhibitors, inclisiran, lomitapide, and evinacumab, which have substantially improved LDL-C control in many patients. However, the effectiveness of these therapies is still greatly dependent on the residual LDL-receptor activity, especially when using receptor-targeted therapies. Conversely, LA provides an immediate and receptor-independent decrease in LDL-C and Lp(a), which continues to play a specific role in severe HoFH, particularly in children, during pregnancy, and when there is a lack of response to the optimal pharmacological treatment. Therefore, modern management is more and more based on a combined approach where LA is added to innovative lipid-lowering drugs, a better time-average LDL-C exposure, and a lower rebound after the treatment. Recent ESC/EAS and AHA guidelines still maintain that LA should be used

Table 3. Effects of Lipoprotein Apheresis

Reduction of LDL-C, LDL-Ox, VLDL-C, Lp(a), PTX3 and coagulation factors levels in plasma
Reduction of plasma viscosity and red blood cell aggregation
Reduction of adhesion molecules and cytokines – pleiotropic or lipid-lowering unrelated
Increased NO availability and improved endothelial function
Delay in the progression of coronary lesions demonstrated by angiographic means
Reduction in ATHS plaque area and calcified plaque volume
Increased coronary reserve
Reduction in IMT in the epiaortic (carotid) vessels
Reduction of cardiac mortality and coronary events

in selected HoFH patients who cannot reach LDL-C targets despite the maximum tolerated medical therapy.

LA is especially applicable in these special clinical units where children with HoFH are treated, as well as during pregnancy, where the number of safe treatments is frequently constrained. The pediatric data reported in Table 2 justify the long-term viability, procedural security, and clinical tolerability of early LA initiation with possible advantages in deferring early atherosclerotic disease development. Similarly, Figure 1 demonstrates the marked LDL-C reduction achievable with LA during pregnancy, emphasizing its practical value when pharmacological options are limited or contraindicated.

In addition to lipid-lowering, LA also has several clinically significant pleiotropic effects, such as inflammatory markers, plasma viscosity, adhesion molecules, and endothelial function improvements, as summarized in Table 3. Even with its proven effectiveness, LA has significant practical constraints, such as procedural invasiveness, in some countries high cost scarce access in specialized facilities, and the necessity of lifetime repetitive sessions, which could adversely impact patient compliance and accessibility. In addition, most of the evidence presently available is observational and based on registry information and long-term clinical experience instead of being based on current randomized trials. However, its sustained, long-term cardiovascular benefits, and the long-term safety data on a large scale have been uniformly consistent, which underlines its relevance in the selective HoFH patients.

Overall, the accumulated evidence of the last 50 years since the original clinical experience of Thompson proves the continuity of the existing and developing therapeutic LA in HoFH, especially in severe phenotypes and special clinical conditions where receptor-independent LDL-C reduction has a unique value.

Competing interests

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