Curr Atheroscler Rep (2015) 17:465
DOI 10.1007/s11883-014-0465-6



# Lipoprotein Apheresis in the Management of Familial Hypercholesterolaemia: Historical Perspective and Recent Advances

**Claudia Stefanutti · Gilbert R. Thompson**

Published online: 20 November 2014


**Abstract** At present, lipoprotein apheresis, combined with high-dose statin and ezetimibe therapy, is the best available means of treating patients with homozygous and statin-refractory heterozygous familial hypercholesterolaemia (FH). However, the extent of cholesterol-lowering achieved is often insufficient to meet the targets set by current guidelines. The recent advent of three new classes of lipid-lowering agents provides new hope that the latter objective may now be achievable. These compounds act either by reducing low-density lipoprotein (LDL) production by inhibiting apolipoprotein B synthesis with an antisense oligonucleotide (mipomersen) or by inhibiting microsomal triglyceride transfer protein (lomitapide), or by enhancing LDL catabolism via monoclonal antibody-mediated inhibition of the activity of proprotein convertase subtilisin/kexin 9 (PCSK9) (evolocumab). Depending on the outcome of current trials, it seems likely that these compounds, used alone or combined with lipoprotein apheresis, will markedly improve the management of refractory FH.

This article is part of the Topical Collection on *New Drugs Approved for Homozygous FH*

C. Stefanutti
Extracorporeal Therapeutic Techniques Unit, Lipid Clinic and Atherosclerosis Prevention Centre, Immunohematology and Transfusion Medicine, 'Umberto I' Hospital, Rome, Italy

C. Stefanutti (✉)
Department of Molecular Medicine, 'Sapienza' University of Rome, Rome, Italy
e-mail: claudia.stefanutti@uniroma1.it

G. R. Thompson
Clinical Lipidology, Hammersmith Hospital, Imperial College London, Ducane Road, London W12 0NN, UK
e-mail: g.thompson@imperial.ac.uk

**Keywords** Low-density lipoprotein · Cholesterol · LDL receptor · Atherosclerosis · Statin · Ezetimibe · Plasmapheresis · Mipomersen · Lomitapide · Evolocumab

## Introduction

Physical removal of cholesterol-rich lipoproteins from the blood stream is usually undertaken only in extreme circumstances, such as in patients with severe, drug-refractory familial hypercholesterolaemia (FH). These are mostly homozygotes, i.e. they possess two mutant alleles for one of the genes known to determine low-density lipoprotein (LDL) uptake by the liver. In 90 % of instances, FH is due to mutations of the LDL receptor gene, leading to either a complete lack or marked reduction of LDL binding and degradation. In such circumstances, drugs like statins that stimulate LDL receptor activity may be ineffective and other methods of lowering LDL cholesterol, such as apheresis, are needed.

Apheresis ( φαίρεσις, to take away) is the term used to describe extracorporeal removal of blood components and has been in use for over 40 years in medical specialties such as haematology, immunology, nephrology and lipidology. The first part of this review describes the history of the extracorporeal removal of LDL and other cholesterol-rich lipoproteins from the circulation and the methods used to achieve this, together with the indications for its use and evidence of benefit. The second part discusses recent advances in lipid-lowering pharmacotherapy that may enhance the efficacy of apheresis or even, in some instances, render it unnecessary.

### Unselective Methods of Apheresis

The first attempt to lower serum cholesterol using manual plasmapheresis was undertaken in London by Myant and Lewis in 1964 in a child with homozygous FH but was

unsuccessful. The following year, De Gennes et al. [1] repeatedly performed manual plasmapheresis in an adult with homozygous FH in Paris. Although this approach reduced the patient's serum cholesterol by 40 %, it was too tedious for prolonged use and was abandoned after 4 months.

The introduction of the continuous-flow blood cell separator revolutionized the situation by enabling large-volume plasma exchanges to be undertaken at high flow rates, using fresh frozen plasma or human serum albumin as replacement fluid. In 1972, Turnberg et al. [2] used a cell separator to plasma exchange a hypercholesterolaemic patient with primary biliary cirrhosis, and 3 years later, Thompson et al. treated two FH homozygotes in a similar manner [3]. Plasma exchange was subsequently used to treat FH homozygotes in South Africa [4] and the USA [5].

## Selective Methods

The first attempt to selectively remove low-density lipoprotein (LDL) extracorporeally involved serial venesection, with ex vivo mixing of heparin-linked agarose beads with batches of blood prior to the latter's re-infusion [6]. Although this selectively bound and removed LDL, the procedure was slower and more cumbersome than plasma exchange. However, in 1981, Stoffel et al. [7] combined the two approaches by using a cell separator to perfuse plasma through a sepharose column containing antibodies that bound LDL, a procedure they termed LDL apheresis. Recently, it was suggested that "lipoprotein apheresis" is a more appropriate term for a procedure that is used for the extracorporeal removal of not only LDL but also chylomicrons, very-low-density lipoprotein (VLDL) and lipoprotein (a) (Lp(a)) [8]. Although plasma exchange is still used in some centres, it is increasingly being replaced by selective lipoprotein apheresis, except when treating severe hypertriglyceridaemia [8].

## Selective Removal from Plasma

### *Immunoadsorption*

As discussed above, selective removal of LDL from plasma using LDL-binding antibodies was the first such method to be developed [7]. The system consists of a continuous-flow cell separator which separates and then pumps plasma through columns containing polyclonal sheep antibodies to human apolipoprotein $B_{100}$ (apoB) coupled with sepharose 4B gel [9]. Anti-coagulation is achieved with heparin and acid citrate dextrose (ACD) and 4–6 L of plasma are treated during each procedure, resulting in 55 % reductions in LDL cholesterol and Lp(a). Columns are regenerated with glycine buffer, flushed with saline and then stored in sodium azide to maintain sterility between procedures.

### *Double Filtration Plasmapheresis and Thermofiltration Plasmapheresis*

The next selective method of removing lipoproteins from plasma to be developed was double filtration plasmapheresis (DFPP) [10]. In this procedure, plasma is separated from blood cells by a hollow fibre filter (first filter) and then perfused through a second filter which selectively retains smaller plasma components such as HDL and albumin but discards larger molecular weight components including LDL and Lp(a). Thermofiltration involves warming plasma to 40 °C prior to DFPP, which increases the amount of LDL removed and reduces the amount of HDL lost [11].

### *Dextran Sulphate Adsorption*

Dextran sulphate covalently bound to cellulose beads selectively binds VLDL and LDL but not HDL. Perfusion of columns containing this material with heparinized plasma separated from blood cells by hollow fibre (membrane) filters provided the first disposable method of LDL apheresis [12]. When twin columns are used alternately to adsorb LDL from plasma, each column being automatically regenerated between successive adsorption cycles, there are no limits to the amount of LDL that can be adsorbed with this system [13].

Studies in FH patients showed acute reductions in LDL cholesterol of 75–80 % and in Lp(a) of 65–70 % [14]. Bi-weekly procedures resulted in average reductions in LDL cholesterol during the interval between procedures (interval mean) of 40–50 % below baseline. A 5-year follow-up, during which almost 4000 procedures were undertaken, showed an adverse event rate of only 3.6 % [15].

### *Heparin Extracorporeal LDL Precipitation*

A radically different approach to LDL apheresis involves the on-line precipitation of LDL through the addition of heparin to plasma, the so-called heparin extracorporeal LDL precipitation (HELP) system [16]. Precipitation of LDL occurs without addition of cations if the pH is sufficiently low, the precipitate being removed by filtration [17]. The plasma is then passed through an adsorption column to remove excess heparin, dialysed against bicarbonate buffer to restore the pH to normal and returned to the patient. This results in acute reductions in LDL cholesterol and Lp(a) of around 60 % [18], accompanied by a 50 % decrease in fibrinogen [16]. Interval means of LDL cholesterol decreased by 33 % during bi-weekly procedures [19]. Side effects were infrequent, and haemorrhagic complications were not observed.

## Selective Removal from Whole Blood

### *Direct Adsorption of Lipoprotein Using Haemoperfusion*

The development of a non-haemolytic adsorber in 1993 enabled removal of LDL and Lp(a) from whole blood, the pore size of the polyacrylate-coated polyacrylamide beads used in the direct adsorption of lipoprotein (DALI) columns being sufficiently small to exclude red cells and platelets [20]. Anti-coagulation was initiated by heparin and maintained by ACD. Passage of 1.6 blood volumes through the adsorber decreased LDL cholesterol and Lp(a) levels by 60–70 % without reducing HDL cholesterol or fibrinogen. Activation of leucocytes and complement was minimal, and the procedure was well tolerated.

### *Dextran Sulphate Adsorption Using Haemoperfusion*

More recently, direct adsorption of lipoproteins from whole blood has also been successfully achieved by haemoperfusion of dextran sulphate-containing columns adapted for this purpose. This involves utilising larger beads (Liposorber D) than those in the standard Liposorber columns used in selective adsorption from plasma [21].

## Comparisons Between Different Methods of Lipoprotein Apheresis

Acute decreases in LDL cholesterol range from 49 to 76 %, depending upon the volume of blood or plasma treated, averaging over 60 % and differ little between the various methods. When interval means rather than acute changes in LDL cholesterol were compared, reductions of 45–52 % from baseline were seen with DALI, dextran sulphate adsorption (DSA) and immunoadsorption (IA) [20].

Although all methods lower LDL cholesterol to a similar extent, the data suggest that DFPP decreases HDL cholesterol more than other methods [22]. Haemoperfusion systems are the easiest to use but, like HELP and DSA, are more expensive than IA with its re-usable columns.

## Vascular Access and Side Effects

Reasonably good vascular access is required for therapeutic plasmapheresis and lipoprotein apheresis. Bilateral antecubital vein cannulation is commonly used. However, when natural vascular access is poor or inefficient from long use (local stenotic fibrosis), surgical preparation of an arteriovenous shunt is required. Arteriovenous shunts are best avoided in children because of their impermanence and the risk of cardiac right ventricular overload. Anticoagulation with citrate and heparin is utilized continuously during the extracorporeal procedure, sometimes preceded by a heparin bolus (IV). Thus, bleeding from vascular access may occur hours after the session, especially if the occlusive dressing is removed prematurely. Beyond possible inconvenience with equipment and vascular access, the overall incidence of clinical side effects with therapeutic plasmapheresis in general and lipoprotein apheresis in particular is relatively low in expert teams, just over 4 % [23]. Non-specific clinical symptoms include fatigue, and nausea, with mild abdominal pain being more frequent in children and hypotensive subjects [24]. Mild hypotension is more common when the extracorporeal volume exceeds over 10 % of total blood volume, without fluid replacement [25]. The only serious adverse event is the occurrence of anaphylactoid reactions in patients on angiotensin-converting enzyme (ACE) inhibitors during DSA procedures. Ionically charged columns, particularly dextran sulphate and polyacrylate gel, convert kininogen to bradykinin, so that concurrent use of ACE inhibitors enhances the effects of bradykinin, which may result in mild-to-severe hypotension and flushing [24, 26]. ACE inhibitors should be suspended at least the day prior to and during apheresis or replaced with angiotensin II receptor blockers (ARB). Anaemia, responsive to iron and folate replacement, is occasionally observed in patients treated on long-term. Lastly, therapeutic apheresis in general and lipoprotein apheresis in particular can safely and effectively be carried out in pregnant women with FH and/or coexistent coronary disease [27].

## Factors Influencing the Need for Lipoprotein Apheresis in Homozygous FH

In an analysis of 57 FH homozygotes, Goldstein and Brown [28] divided them into receptor negative and receptor defective categories according to whether their cultured fibroblasts showed no high-affinity binding of LDL (<2 % of normal) or whether they bound a subnormal amount (2–25 %). As shown in Table 1, the frequency of coronary disease was similar in the two groups (45 and 42 %, respectively) but mortality was much higher in the 31 receptor negative subjects than in the 26 who were receptor defective (26 versus 4 %). Presumably, this reflected more severe atherosclerosis among the former, predicated on the assumption that they had higher serum cholesterol levels. This assumption is supported by South African data, where homozygotes whose fibroblasts bound LDL with

**Table 1** Mortality and coronary heart disease morbidity in receptor-negative and receptor-defective FH homozygotes (based on data from Goldstein and Brown [24])

| LDL receptor status | Number of subjects | Coronary heart disease (%) | Mortality (%) |
|---|---|---|---|
| Negative | 31 | 45 | 26 |
| Defective | 26 | 42 | 4 |

<5 % of the efficiency of normal fibroblasts had an LDL cholesterol of 25 mmol/L compared with 17 mmol/L in homozygotes whose fibroblasts expressed 5–20 % of normal LDL-binding activity [29].

Guatschi et al. [30••] recorded seven cases of FH homozygotes dying before the age of 5, and there has been at least one additional instance of this (Coote, personal communication). Pre-treatment serum cholesterol of these eight cases averaged 25.1 mmol/L, and their mean age of death was 3.3 years. At the other end of the spectrum, there are five reported instances of FH homozygotes surviving past the age of 50 [31, 32•, 33••] plus an unpublished case (Thompson, personal communication), three of the six being still alive. Their mean age now or at death is 59.5 years, and their mean pre-treatment serum cholesterol was 16.0 mmol/L, considerably lower than the homozygotes who died before the age of 5.

Overall, these observations suggest that a major determinant of the cardiovascular consequences and prognosis of FH homozygotes is the severity of their hypercholesterolaemia. The risk of premature death and need for apheresis appear to be greatest in homozygotes with an untreated serum cholesterol of >20 mmol/L, especially those who are receptor negative. In contrast, South African homozygotes, the majority of whom are receptor defective and have a pre-treatment serum cholesterol of <20 mmol/L [29], respond reasonably well to high-dose statin±ezetimibe therapy [34••].

## Evidence of Benefit from Lipoprotein Apheresis

### *Homozygous FH*

The first evidence of benefit from lipoprotein apheresis came from studies in five sibling pairs of homozygotes. All the untreated siblings had died (mean age of death 17.7), whereas four of the five siblings treated for 8.4 years with plasma exchange survived, with a mean age of 23.2 at the time of the report ($P$=0.03) [35]. In a longer observational study of German patients, mortality was 43 % among the seven untreated homozygotes compared with 21 % in the 14 treated with lipoprotein apheresis for ≥1 year [31].

Another more recent observational study involved 149 South African homozygotes, 15 % of whom were undergoing apheresis. This showed that the average age of death rose from 18.4 years in the pre-statin era to 32.9 years ($P$<0.0001) after these drugs became available; this was attributed to the 26 % lowering of LDL cholesterol during the latter period [34••].

### *Heterozygous FH*

Lipoprotein apheresis is also used to treat patients with drug-refractory heterozygous FH and progressive coronary disease. Results of three angiographic trials in 117 patients showed decreases in LDL cholesterol on drug therapy of 34–47 % compared with 43–63 % on apheresis±drugs [36–38]. Quantitative angiography showed no change or regression of coronary lesions over the course of 2 years in 36–79 % of patients on drug therapy alone compared with 57–92 % in those on apheresis±drugs, but the differences between treatment groups were significant ($P$<0.004) only in L-CAPS (38).

In a non-randomized study of 130 Japanese heterozygotes lasting 10 years, reductions in LDL cholesterol averaged 28 % on drugs compared with 58 % in those on apheresis plus drugs [39]. The incidence of coronary events was 36 % on drug therapy compared with only 10 % in those on apheresis plus drugs ($P$<0.01). Taken together, these data suggest that apheresis exerts beneficial effects on cardiovascular disease in heterozygotes as well as in homozygotes.

## Guidelines and Target Levels for Lipoprotein Apheresis

Guidelines on the use of lipoprotein apheresis to treat FH have been published in the USA [40–42, 43••], Europe [44–47], Japan [48•] and the UK [22]. In 2008, the Food and Drug Administration (FDA) approved the use of apheresis in three categories of patients in the USA:

(a) Functional FH homozygotes with LDL-C >500 mg/dL (>13 mmol/L)
(b) Functional FH heterozygotes with LDL-C >300 mg/dL (>7.8 mmol/L)
(c) Functional FH heterozygotes with LDL-C >200 mg/dL (>5.2 mmol/L) and documented coronary heart disease

In each instance, these cut-offs must be exceeded despite 6 months of diet and maximum tolerated drug therapy.

For homozygotes, the HEART UK guidelines advocate treating 1.5–2 blood or plasma volumes at weekly or bi-weekly intervals so as to achieve an interval mean total cholesterol of <7 mmol/L or LDL cholesterol <6.5 mmol/L (or decreases of >60 or 65 %, respectively, from baseline levels off all treatment). However, data on the occurrence of cardiovascular disease in 64 French [49] and US [50, 51] homozygotes undergoing long-term apheresis cast doubt on those recommendations. In these studies, baseline levels of total or LDL cholesterol off all treatment exceeded 20 mmol/L and were reduced by 45–55 % by apheresis plus lipid-lowering drug therapy. In the French patients [49] and in a US subgroup treated in New York [50], the calculated interval mean values of LDL cholesterol were 6.6 and 6.5 mmol/L, respectively, namely a 64–69 % reduction from baseline levels off all treatment. Aortic root and coronary atherosclerosis was present in roughly half of the patients prior to apheresis and a further 20–35 % of patients developed new lesions or showed progression of pre-existing ones while on apheresis, despite the marked reductions in LDL cholesterol that occurred.

In an Italian study of 11 homozygous children aged 3–11 treated with weekly or biweekly lipoprotein apheresis, baseline LDL cholesterol levels were reduced by 60 % from 19.8 mmol/L off treatment to 8.0 mmol/L on apheresis. However, in contrast to the previously cited US and French studies, more than two thirds of the patients remained lesion-free during 2–17 years of follow-up and more than 60 % of the remainder showed regression or non-progression of pre-existing aorto-coronary lesions on serial angiography [52]. These results illustrate the importance of starting treatment as early as possible.

Another, more recent study has shown that achieving an interval mean LDL cholesterol of 4.2 mmol/L by weekly apheresis plus statin/ezetimibe therapy failed to prevent progression of aortic, coronary and carotid disease in Norwegian homozygotes who started apheresis between the ages of 6–44, suggesting that even lower levels of LDL are required in older patients [33••]. This is reflected in the most recent statement on target levels for both homozygous and heterozygous FH, which advocates lowering LDL cholesterol to <3.5 mmol/L in children and to <2.5 mmol/L in adults, or even <1.8 mmol/L in those at the highest risk [53••]. Although desirable, these levels can seldom be achieved in homozygotes with existing apheresis/drug therapy regimens and novel therapies are needed, as discussed in the second part of this review.

## Recent Advances

### Current Therapy

Current drug therapy for homozygous FH consists of anion-exchange resins and, more recently, of ezetimibe and HMGCoA-reductase inhibitors (statins) at maximum tolerated doses [54–57]. The combination of atorvastatin 80 mg and ezetimibe 10 mg daily resulted in an additional 27.5 % reduction in LDL cholesterol in FH homozygotes on lipoprotein apheresis [54], but this seldom brings LDL cholesterol to target in these very high-risk patients. This underlines the need to develop other LDL cholesterol-lowering agents to be used with or instead of lipoprotein apheresis. At present, apheresis is usually carried out every 2 weeks, but in a minority every week [58, 22]. The frequency of the extracorporeal procedure is determined by the severity of the atherosclerotic involvement of coronary arteries and aortic valve and evidence of progression [59, 60, 39, 34••]. This being so, serial evaluation and follow-up of the cardiovascular status of homozygous FH patients on long-term treatment is mandatory [52].

An alternative treatment is liver transplantation. However, this poses serious problems in respect of the availability of organs and risks associated with the intervention; these include life-long immunosuppressive therapy and possible chronic rejection and the fact that the LDL-receptor is not solely located in the liver [61, 62]. This means that a residual dyslipidaemia might persist, possibly aggravated by long-term immunosuppression, requiring further lipid-lowering treatment. Lastly, the prognosis of liver transplantation in the medium to long-term is limited by concurrent cardiovascular disease [63]. Gene therapy has also been attempted to correct the genetic defect in homozygous FH [64, 65], but the outcomes were not very encouraging [66, 67•]. Thus at present, gene therapy remains a putative therapeutic approach that may or may not become available in the future.

Lipoprotein apheresis is currently the only really safe and effective treatment for homozygous FH [68••], combined with additional drug therapy to slow down the rapid rebound of LDL cholesterol which follows each procedure. The intention is to keep the LDL cholesterol level as low as possible for as long as possible [69•]. In a Japanese study, the cholesterol absorption inhibitor ezetimibe was given to six FH homozygotes undergoing apheresis and receiving atorvastatin or simvastatin [70]. With the exception of one patient, LDL-C was reduced by ezetimibe to a statistically significant extent 2 weeks after each apheresis session. The average reduction was 9.0 % (range 4.3–12.6 %). The authors concluded that although the effect of ezetimibe was not impressive, its use in combination with statins in the treatment of homozygotes undergoing lipoprotein apheresis was clinically relevant, as demonstrated previously by Gagné et al. [54].

### Future Prospects

Excitingly, the management of homozygous FH by pharmacological means is now at a new frontier because of the emergence of novel and potent compounds which reduce LDL production by limiting apolipoprotein B100 (apoB) synthesis, either by means of an antisense oligonucleotide to apoB (mipomersen) or by inhibition of microsomal triglyceride transfer protein (MTP) (lomitapide), or which enhance LDL catabolism by inhibiting the activity of proprotein convertase subtilisin/kexin 9 (PCSK9) [71, 72•, 73••, 74, 75•, 76]. These compounds are described in detail elsewhere in this issue of the journal, but their role in the treatment of homozygous FH is summarized below.

At the end of 2012, the US Food and Drug Administration (FDA) approved two new cholesterol-lowering agents based on apoB synthesis inhibition, one the antisense oligonucleotide mipomersen and the other the MTP inhibitor lomitapide, for the treatment of homozygous FH patients [77, 78]. In 2010, a phase three randomized, double-blind, placebo-controlled clinical trial of mipomersen for the treatment of homozygous FH patients was reported [79]. The study was aimed at investigating the effectiveness and safety of a weekly subcutaneous injection of mipomersen 200 mg given as an add-on treatment to optimal standard lipid-lowering therapy for 26 weeks. However, patients on lipoprotein apheresis were

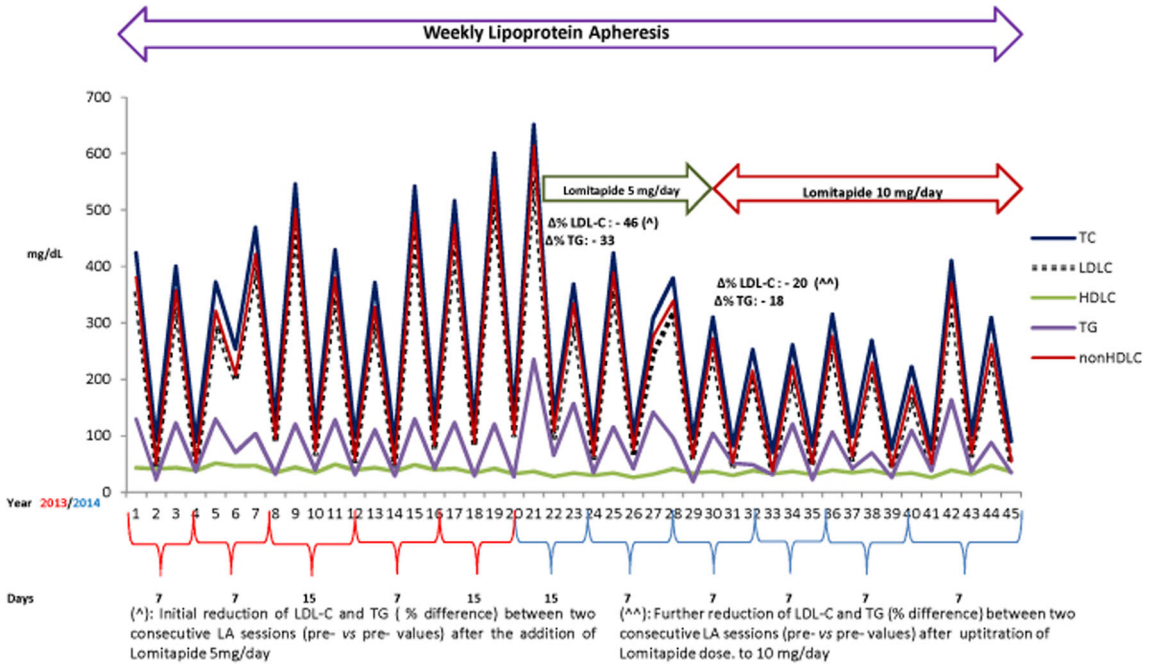


**Fig. 1** Effect on serum lipids of adding lomitapide 5 and 10 mg/day to weekly lipoprotein apheresis in a 22-year-old female with homozygous FH. *(^)* indicates the % reduction of LDL-C and TG between two consecutive apheresis sessions (pre- versus pre-values) after the addition of lomitapide 5 mg/day. *(^^)* indicates the additional % reduction of LDL-C and TG between two consecutive apheresis sessions (pre- versus pre-values) after up titration of lomitapide to 10 mg/day

excluded. The intention-to-treat analysis showed a statistically significant reduction in LDL-C of 24.7 % in patients treated with mipomersen. The most common adverse events observed with mipomersen were reactions at the injection site, flu-like symptoms and increased transaminases.

In 2013, Cuchel et al. reported the results of a single-arm, open-label, phase three study of lomitapide in 29 female and male FH homozygotes [80••]. Pre-existing lipid-lowering therapy was maintained from 6 weeks before the start of this trial and maintained until at least week 26. Eighteen of the patients were on lipoprotein apheresis during this phase of the study. The dose of lomitapide was progressively up titrated on the basis of safety and tolerability from 5 mg to a maximum of 60 mg a day, the median dose being 40 mg a day. LDL cholesterol was reduced by 50 % from basal values (mean 8.7 mmol/L) to week 26 (4.3 mmol/L). Furthermore, 16 subjects on lomitapide achieved LDL cholesterol target levels <2.6 mmol/L and 9 achieved levels <1.8 mmol/L. Reductions in LDL cholesterol by lomitapide were similar in patients on or not on apheresis. The most common adverse events were gastrointestinal symptoms and increased transaminase levels, which were reversible after dose reduction or temporary interruption of lomitapide. The effect of combined treatment consisting of weekly apheresis and lomitapide given at a dose of 5 mg/day, later up titrated to 10 mg/day, in a 22-year-old female homozygote (FH), who underwent aortic and mitral valve replacement, is shown in Fig. 1.

Monoclonal antibodies (mAbs) directed against PCSK9 are currently in clinical development. Stein et al. [81••] investigated the efficacy and safety of the experimental monoclonal antibody evolocumab (AMG 145) in an open-label, single-arm, multicenter, pivotal study in homozygous FH patients. Eight patients with receptor-negative or receptor-defective homozygous FH on stable lipid-lowering drug therapy were treated with 420 mg AMG 145 given subcutaneously every 4 weeks for ≥12 weeks, followed by 420 mg AMG 145 every 2 weeks for a further 12 weeks. Patients receiving lipoprotein apheresis within 8 weeks of the screening visit, those

**Table 2** Published data on effect of current and novel drugs on percentage reduction in LDL cholesterol (LDL-C) in FH homozygotes

| Author | Year | Number of subjects | Drug | LDL-C reduction % |
|---|---|---|---|---|
| Gagné et al. | 2002 | 50 | Ezetimibe+atorvastatin/simvastatin | −27.5 |
| Yamamoto et al. | 2006 | 6 | Ezetimibe+atorvastatin/simvastatin | −9.0 |
| Raal et al. | 2010 | 34 | Mipomersen | −24.7 |
| Cuchel et al. | 2013 | 29 | Lomitapide | −50 |
| Stein et al. | 2013 | 8 | Evolocumab | −16.5 |

scheduled to receive lipoprotein apheresis during the study and those treated with mipomersen or lomitapide within 5 months of screening were excluded. Over the treatment periods, LDL cholesterol levels in the six LDL receptor-defective patients decreased by 19.3 and 26.3 % with 4- and 2-week dosing, respectively. No effect of evolocumab was observed in the two receptor-negative subjects. The most common adverse events of evolocumab were upper respiratory tract infections, influenza, gastroenteritis and nasopharyngitis. The effects of conventional and novel drug regimens on reduction of LDL cholesterol levels in FH homozygotes are compared in Table 2.

## Conclusions

Historically, extracorporeal removal of cholesterol-carrying lipoproteins from the blood was first introduced more than 40 years ago. Initially, this entailed the non-selective procedure of plasma exchange, but subsequently, this was replaced by the selective removal from plasma or blood of low-density lipoproteins, notably LDL and Lp(a), by lipoprotein apheresis. When combined with high-dose statin and ezetimibe therapy weekly or bi-weekly apheresis decreases the interval mean levels of these atherogenic lipoproteins by 60–70 %, with much smaller reductions in HDL.

Observational data demonstrate that this therapeutic approach reduces progression of aortic and coronary atherosclerosis and increases longevity in homozygous FH and reduces coronary events in FH heterozygotes. However, target levels of LDL cholesterol stipulated in recent guidelines are hard to achieve, especially in receptor-negative homozygotes, and a new approach is needed.

At the end of 2012 and start of 2013, respectively, the FDA approved the use of oral lomitapide (Juxtapid, Lojuxta) and of subcutaneously administered mipomersen (Kynamro) to treat patients with homozygous FH in the USA [77, 78]. In August 2013, the European Commission approved the use of lomitapide (but not mipomersen) for this purpose in Europe [82••]. The pharmacological management of homozygous FH is at a new frontier with the advent of these potent cholesterol-lowering drugs [71, 72•, 73••, 83•, 84, 85•]. However, although promising, these new lipid-lowering drugs must be carefully clinically evaluated in terms of efficacy on cardiovascular morbidity and mortality and safety. Long-term studies on the incidence of adverse events, in particular the extent of fat accumulation in the liver and possible drug-drug interactions, need to be carried out. Clinical trials of the new drugs in homozygous children are also needed, since therapeutic intervention in these very high-risk patients should be initiated as early as possible. Lastly, it is necessary to consider whether the high cost of these new drugs is affordable by national health systems in Europe and elsewhere. For the present, lipoprotein apheresis in combination with conventional pharmacological treatment remains the best proven, most effective and safest approach to treating refractory FH [86•, 87••].

### Compliance with Ethics Guidelines

**Conflict of Interest** Claudia Stefanutti received personal fees from Kaneka Pharma NV Europe and Aegerion. Gilbert R. Thompson serves on the advisory board for Aegerion.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

## References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance


1. de Gennes JL, Touraine R, Maunand B, Truffert J, Laudat P. Homozygous cutaneo-tendinous forms of hypercholesteremic xanthomatosis in an exemplary familial case. Trial of plasmapheresis an heroic treatment. Bull Mem Soc Med Hôp Paris. 1967;118:1377–402.
2. Turnberg LA, Mahoney MP, Gleeson MH, Freeman CB, Gowenlock AH. Plasmapheresis and plasma exchange in the treatment of hyperlipaemia and xanthomatous neuropathy in patients with primary biliary cirrhosis. Gut. 1972;13:976–81.
3. Thompson GR, Lowenthal R, Myant NB. Plasma exchange in the management of homozygous familial hypercholesterolaemia. Lancet. 1975;l:l208–11.
4. Berger GM, Miller JL, Bonnici F, Joffe HS, Dubovsky DW. Continuous flow plasma exchange in the treatment of homozygous familial hypercholesterolemia. Am J Med. 1978;65:243–51.
5. King ME, Breslow JL, Lees RS. Plasma-exchange therapy of homozygous familial hypercholesterolemia. N Engl J Med. 1980;302:1457–9.
6. Lupien PJ, Moorjani S, Awad J. A new approach to the management of familial hypercholesterolaemia: removal of plasma-cholesterol based on the principle of affinity chromatography. Lancet. 1976;1:1261–5.
7. Stoffel W, Borberg H, Greve V. Application of specific extracorporeal removal of low density lipoprotein in familial hypercholesterolaemia. Lancet. 1981;2:1005–7.
8. Thompson GR. Lipoprotein apheresis. Curr Opin Lipidol. 2010;21:487–91.
9. Richter WO, Jacob BG, Ritter MM, Sühler K, Vierneisel K, Schwandt P. Three-year treatment of familial heterozygous hypercholesterolemia by extracorporeal low-density lipoprotein immunoadsorption with polyclonal apolipoprotein B antibodies. Metabolism. 1993;42:888–94.
10. Agishi T, Kaneko I, Hasuo Y, et al. Double filtration plasmapheresis. Trans Am Soc Artif Intern Organs. 1980;26:406–11.
11. Klingel R, Mausfeld P, Fassbender C, Goehlen B. Lipidfiltration—safe and effective methodology to perform lipid-apheresis. Transfus Apher Sci. 2004;30:245–54.

12. Yokoyama S, Hayashi R, Satani M, Yamamoto A. Selective removal of low density lipoprotein by plasma pheresis in familial hypercholesterolemia. Arteriosclerosis. 1985;5:613–22.
13. Mabuchi H, Michishita I, Takeda M, et al. A new low density lipoprotein apheresis system using two dextran sulfate cellulose columns in an automated column regenerating unit (LDL continuous apheresis). Atherosclerosis. 1989;68:19–26.
14. Gordon BR, Kelsey SF, Bilheimer DW, et al. Treatment of refractory familial hypercholesterolemia by low-density lipoprotein apheresis using an automated dextran sulfate cellulose adsorption system. Am J Cardiol. 1992;70:1010–6.
15. Gordon BR, Kelsey SF, Dau PC, for the Liposorber Study Group, et al. Long-term effects of low-density lipoprotein apheresis using an automated dextran sulfate cellulose adsorption system. Am J Cardiol. 1998;81:407–11.
16. Eisenhauer T, Armstrong VW, Wieland H, Fuchs C, Scheler F, Seidel D. Selective removal of low density lipoproteins (LDL) by precipitation at low pH; first clinical application of the HELP system. Klin Wochenschr. 1987;65:161–8.
17. Armstrong VW, Windisch M, Wieland H, et al. Selective continuous extracorporeal elimination of low-density lipoproteins with heparin at acidic pH. Trans Am Soc Artif Intern Organs. 1983;29:323–8.
18. Armstrong VW, Schuff-Werner P, Eisenhauer T, Helmhold M, Stix M, Seidel D. Heparin extracorporeal LDL precipitation (HELP): an effective apheresis procedure for lowering Lp(a) levels. Chem Phys Lipids. 1994;67–68:315–21.
19. Lane D, McConathy WJ, Laughlin LO, et al. Selective removal of plasma low density lipoprotein with the HELP system: biweekly versus weekly therapy. Atherosclerosis. 1995;114:203–11.
20. Bosch T, Schmidt B, Blumenstein M, Gurland HJ. Lipid apheresis by hemoperfusion: in vitro efficacy and ex vivo biocompatibility of a new low-density lipoprotein adsorber compatible with human whole blood. Artif Organs. 1993;17:640–52.
21. Julius U, Parhofer KG, Heibges A, Kurz S, Klingel R, Geiss HC. Dextran-sulfate-adsorption of atherosclerotic lipoproteins from whole blood or separated plasma for lipid-apheresis—comparison of performance characteristics with DALI and Lipidfiltration. J Clin Apher. 2007;22:215–23.
22. Thompson GR, HEART-UK LDL Apheresis Working Group. Recommendations for the use of LDL apheresis. Atherosclerosis. 2008;198:247–55.
23. Richter WO, Donner MG, Schwandt P. Three low density lipoprotein apheresis techniques in treatment of patients with familial hypercholesterolemia: a long-term evaluation. Ther Apher. 1999;3:203–8.
24. Watts GF, Hamilton SJ. LDL apheresis for familial hypercholesterolemia: value, indications and demand. Clin Lipidol. 2009;4:129–31.
25. Stefanutti C, Lanti A, Di Giacomo S, et al. Therapeutic apheresis in low weight patients: technical feasibility, tolerance, compliance, and risks. Transfus Apher Sci. 2004;31:3–10.
26. Sinzingera H, Bednar J, Granegger S, Blazek I, Peskar BA. LDL-apheresis and concomitant ACE-inhibitor therapy. Atherosclerosis. 1994;105:115–6.
27. Cashin-Hemphill L, Noone M, Abbott JF, Waksmonski CA, Lees RS. Low-density lipoprotein apheresis therapy during pregnancy. Am J Cardiol. 2000;86:1160. *A10*.
28. Goldstein JL, MS B. The LDL receptor defect in familial hypercholesterolemia. Implications for pathogenesis and therapy. Med Clin N Am. 1982;66:335–62.
29. van der Westhuyzen DR, Coetzee GA, Demasius IP, Harley EH, Gevers W, Baker SG, et al. Low density lipoprotein receptor mutations in South African homozygous familial hypercholesterolemic patients. Arteriosclerosis. 1984;4:238–47.
30.•• Gautschi M, Pavlovic M, Nuoffer JM. Fatal myocardial infarction at 4.5 years in a case of homozygous familial hypercholesterolaemia. JIMD Rep. 2012;2:45–50. *Describes seven cases of extremely premature mortality in FH homozygotes*.
31. Keller C. LDL-Apheresis in homozygous LDL-receptor-defective familial hypercholesterolemia: the Munich experience. Atheroscler Suppl. 2009;10:21–6.
32.• Mabuchi H, Nohara A, Noguchi T, et al. Molecular genetic epidemiology of homozygous familial hypercholesterolemia in the Hokuriku district of Japan. Atherosclerosis. 2011;214:404–7. *This paper describes the clinical and molecular characteristics of 25 FH homozygotes in the Hokuriko district of Japan, 3 of whom lived past the age of 50*.
33.•• Graesdal A, Bogsrud MP, Holven KB, et al. Apheresis in homozygous familial hypercholesterolemia: the results of a follow-up of all Norwegian patients with homozygous familial hypercholesterolemia. J Clin Lipidol. 2012;6:331–9. *Description of progression of cardiovascular disease in FH homozygotes in Norway despite rigorous lipoprotein apheresis and drug therapy*.
34.•• Raal FJ, Pilcher GJ, Panz VR, et al. Reduction in mortality in subjects with homozygous familial hypercholesterolemia associated with advances in lipid-lowering therapy. Circulation. 2011;124:2202–7. *Comparison of serum cholesterol levels and mortality in FH homozygotes in South Africa in the pre- and post-statin eras*.
35. Thompson GR, Miller JP, Breslow JL. Improved survival of patients with homozygous familial hypercholesterolaemia treated by plasma exchange. Br Med J. 1989;291:1671–3.
36. Thompson GR, Maher VM, Matthews S, et al. Familial hypercholesterolaemia regression study: a randomised trial of low-density-lipoprotein apheresis. Lancet. 1995;345:811–6.
37. Kroon AA, Aengevaeren WR, van der Werf T, LDL-Apheresis Atherosclerosis Regression Study (LAARS), et al. Effect of aggressive versus conventional lipid lowering treatment on coronary atherosclerosis. Circulation. 1996;93:1826–35.
38. Nishimura S, Sekiguchi M, Kano T, et al. Effects of intensive lipid lowering by low-density lipoprotein apheresis on regression of coronary atherosclerosis in patients with familial hypercholesterolemia: Japan Low-density Lipoprotein Apheresis Coronary Atherosclerosis Prospective Study (L-CAPS). Atherosclerosis. 1999;144:409–17.
39. Mabuchi H, Koizumi J, Shimizu M, Hokuriku-FH-LDLApheresis Study Group, et al. Long-term efficacy of low-density lipoprotein apheresis on coronary heart disease in familial hypercholesterolemia. Am J Cardiol. 1998;82:1489–95.
40. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III) final report. Circulation. 2002;106:3143–421.
41. Kavey R-E W, Allada V, Daniels SR, et al. Cardiovascular risk reduction in high-risk pediatric patients. A scientific statement from the american heart association expert panel on population and prevention science; the councils on cardiovascular disease in the young, epidemiology and prevention, nutrition, physical activity and metabolism, high blood pressure research, cardiovascular nursing, and the kidney in heart disease; and the interdisciplinary working group on quality of care and outcomes research. Circulation. 2006;114:2710–38.
42. Sczepiorkowski ZM, Bandarenko M, Kim HC, et al. Guidelines on the use of therapeutic apheresis in clinical practice—evidence-based approach from the apheresis applications committee of the American society for apheresis. J Clin Apher. 2007;22:106–75.
43.•• Ito MK, McGowan MP, Moriarty PM, National Lipid Association Expert Panel on Familial Hypercholesterolemia. Management of familial hypercholesterolemias in adult patients: recommendations from the national lipid association expert panel on familial

hypercholesterolemia. J Clin LipidoI. 2011;5:S38–45. *US guidelines on therapeutic management of FH.*
44. Prevention of coronary heart disease in clinical practice. Recommendations of the Second Joint Task Force of European and other Societies on coronary prevention. Eur Heart J. 1998;19:1434–1503.
45. Gemeinsamer-Bundesausschuss. Bekanntmachung eines Beschlusses des Gemeinsamen Bundesausschusses über eine Änderung der Richtlinie Methoden vertragsärztliche Versorgung: Apherese bei isolierter Lp(a)-Erhöhung für Studienteilnehmer. BAnz 2009;128:3005.
46. Civiera F, for International Panel on Management of Familial Hypercholesterolemia. Guidelines for the diagnosis and management of heterozygous familial hypercholesterolemia. Atherosclerosis. 2004;173:55–68.
47. Stefanutti C. The 2009 2nd Italian consensus conference on LDL-apheresis. Nutr Metab Cardiovasc Dis. 2010;20:761–2.
48.• Harada-Shiba M, Arai H, Oikawa S, et al. Guidelines for the management of familial hypercholesterolemia. J Atheroscler Thromb. 2012;19:1043–60. *Japanese guidelines on the therapeutic management of FH.*
49. Palcoux J-B, Atassi-Dumont M, Lefevre P, et al. Low-density lipoprotein apheresis in children with familial hypercholesterolemia: follow-up to 21 years. Ther Apher Dial. 2008;12:195–201.
50. Hudgins L, Kleimann B, Scheuer A, White S, Gordon BR. Long-term safety and efficacy of low-density lipoprotein apheresis in childhood for homozygous familial hypercholesterolemia. Am J Cardiol. 2008;102:1199–204.
51. Kolansky DM, Cuchel M, Clark BJ, et al. Longitudinal evaluation and assessment of cardiovascular disease in patients with homozygous familial hypercholesterolemia. Am J Cardiol. 2008;102:1438–43.
52. Stefanutti C, Vivenzio A, Giacomo S, et al. Aorta and coronary angiographic follow-up of children with severe hypercholesterolemia treated with low-density lipoprotein apheresis. Transfusion. 2009;49:1461–70.
53.•• Nordestgaard BG, Chapman MJ, Humphries SE, et al. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease. Consensus Statement of the European Atherosclerosis Society. Eur Heart J. 2013;34:3478–90. *Latest European guidelines on the therapeutic management of FH.*
54. Gagné C, Gaudet D, Bruckert E, et al. Efficacy and safety of ezetimibe coadministered with atorvastatin or simvastatin in patients with homozygous familial hypercholesterolemia. Circulation. 2002;105:2469–75.
55. Raal FJ, Pilcher GJ, Illingworth DR, et al. Expanded-dose simvastatin is effective in homozygous familial hypercholesterolaemia. Atherosclerosis. 1997;135249–56.
56. Marais AD, Blom DJ, Firth JC. Statins in homozygous familial hypercholesterolemia. Curr Atheroscler Rep. 2002;4:19–25.
57. Naoumova RP, Thompson GR, Soutar AK. Current management of severe homozygous hypercholesterolaemias. Curr Opin Lipidol. 2004;15:413–22.
58. Gordon BR. Incorporation of low-density lipoprotein apheresis into the treatment program of patients with severe hypercholesterolemia. Curr Atheroscler Rep. 2000;2:308–13.
59. Kawaguchi A, Miyatake K, Yutani C, et al. Characteristic cardiovascular manifestation in homozygous and heterozygous familial hypercholesterolemia. Am Heart J. 1999;137:410–8.
60. Awan Z, Alrasadi K, Francis GA, et al. Vascular calcifications in homozygote familial hypercholesterolemia. Arterioscler Thromb Vasc Biol. 2008;28:777–85.
61. Bilheimer DW, Goldstein JL, Grundy SM, Starzl TE, Brown MS. Liver transplantation to provide low-density-lipoprotein receptors and lower plasma cholesterol in a child with homozygous familial hypercholesterolemia. N Engl J Med. 1984;311:1658–64.
62. Revell SP, Noble-Jamieson G, Johnston P, Rasmussen A, Jamieson N, Barnes ND. Liver transplantation for homozygous familial hypercholesterolaemia. Arch Dis Child. 1995;73:456–8.
63. Kakaei F, Nikeghbalian S, Kazemi K, et al. Liver transplantation for homozygous familial hypercholesterolemia: two case reports. Transplant Proc. 2009;41:2939–41.
64. Grossman M, Raper SE, Kozarsky K, et al. Successful ex vivo gene therapy directed to liver in a patient with familial hypercholesterolaemia. Nat Genet. 1994;6:335–41.
65. Raper SE, Grossman M, Rader DJ, et al. Safety and feasibility of liver-directed ex vivo gene therapy for homozygous familial hypercholesterolemia. Ann Surg. 1996;223:116–26.
66. Rader DJ. Gene therapy for familial hypercholesterolemia. Nutr Metab Cardiovasc Dis. 2001;11 Suppl 5:40–4.
67.• Van Craeyveld E, Jacobs F, Gordts SC, De Geest B. Gene therapy for familial hypercholesterolemia. Curr Pharm Des. 2011;17:2575–91. *Review on experimental LDLr gene transfer studies demonstrating regression of atherosclerosis in experimental models.*
68.•• Thompson GR. The evidence-base for the efficacy of lipoprotein apheresis in combating cardiovascular disease. Atheroscler Suppl. 2013;14:67–70. *Latest evidence-based review on lipoprotein apheresis.*
69.• Stefanutti C, Julius U. Lipoprotein apheresis: state of the art and novelties. Atheroscler Suppl. 2013;14:19–27. *Review and update on recent indications of lipoprotein apheresis and prospects of novel lipid-altering drugs for the treatment of severe dyslipidaemia.*
70. Yamamoto A, Harada-Shiba M, et al. The effect of ezetimibe on serum lipids and lipoproteins in patients with homozygous familial hypercholesterolemia undergoing LDL-apheresis therapy. Atherosclerosis. 2006;186:126–31.
71. Bays H, Stein EA. Pharmacotherapy for dyslipidaemia–current therapies and future agents. Expert Opin Pharmacother. 2003;4:1901–38.
72.• Stefanutti C, Morozzi C, Di Giacomo S. New clinical perspectives of hypolipidemic drug therapy in severe hypercholesterolemia. Curr Med Chem. 2012;19:4861–8. *Review and update of novel lipid-altering drugs for treatment of lipid metabolism disorders.*
73.•• Bell DA, Hooper AJ, Watts GF, Burnett JR. Mipomersen and other therapies for the treatment of severe familial hypercholesterolemia. Vasc Health Risk Manag. 2012;8:651–9. *Recent review on mipomersen for the treatment of severe FH.*
74. Cuchel M, Bloedon LT, Szapary PO, et al. Inhibition of microsomal triglyceride transfer protein in familial hypercholesterolemia. N Engl J Med. 2007;356:148–56.
75.• Hooper AJ, Burnett JR. Anti-PCSK9 therapies for the treatment of hypercholesterolemia. Expert Opin Biol Ther. 2013;13:429–35. *The review summarizes the latest findings in clinical trials of PCSK9 inhibitors, including antibodies, gene silencing and small peptides.*
76. Visser ME, Kastelein JJ, Stroes ES. Apolipoprotein B synthesis inhibition: results from clinical trials. Curr Opin Lipidol. 2010;21:319–23.
77. U.S. Food and Drug Administration. FDA approves new orphan drug for rare cholesterol disorder. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm333285.htm.
78. U.S. Food and Drug Administration. FDA approves new orphan drug Kynamro to treat inherited cholesterol disorder. http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm337195.htm.
79. Raal FJ, Santos RD, Blom DJ, et al. Mipomersen, an apolipoprotein B synthesis inhibitor, for lowering of LDL cholesterol concentrations in patients with homozygous familial hypercholesterolaemia: a randomised, double-blind, placebo-controlled trial. Lancet. 2010;375:998–1006.
80.•• Cuchel M, Meagher EA, du Toit Theron H, et al. 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. *Phase 3 multicentre study on treatment of homozygous FH individuals with Lomitapide.*

81.•• Stein EA, Honarpour N, Wasserman SM, Xu F, Scott R, Raal FJ. Effect of the proprotein convertase subtilisin/kexin 9 monoclonal antibody, AMG 145, in homozygous familial hypercholesterolemia. Circulation. 2013;128:2113–20. *First clinical trial of PCSK9 inhibitor AMG 145 in homozygous FH subjects*.

82.•• European Medicines Agency, European public assessment report (EPAR) EMA/519736/2013 EMEA/H/C/002578, pp 1–3. 18. *Statement of approval of Lojuxta (lomitapide) as an adjunct to a low-fat diet and other lipid-lowering medicinal products with or without LDL-apheresis, issued by the European Commission.*

83.• Roth EM, McKenney JM, Hanotin C, Asset G, Stein EA. Atorvastatin with or without an antibody to PCSK9 in primary hypercholesterolemia. N Engl J Med. 2012;367:1891–900. *Randomized clinical trial involving patients with primary hypercholesterolemia, adding a PCSK9 inhibitor to either 10 mg of atorvastatin or 80 mg of atorvastatin*.

84. Nachimuthu S, Raggi P. Novel agents to manage dyslipidemias and impact atherosclerosis. Cardiovasc Hematol Disord Drug Targets. 2006;6:209–17.

85.• Vuorio A, Tikkanen MJ, Kovanen PT. Inhibition of hepatic microsomal triglyceride transfer protein—a novel therapeutic option for treatment of homozygous familial hypercholesterolemia. Vasc Health Risk Manag. 2014;10:263–70. *Review on lomitapide as novel therapeutic option for treatment of HoFH subjects.*

86.• Page MM, Bell DA, Hooper AJ, Watts GF, Burnett JR. Lipoprotein apheresis and new therapies for severe familial hypercholesterolemia in adults and children. Best Pract Res Clin Endocrinol Metab. 2014;28:387–403. *This review describes the rationale and role of lipoprotein apheresis in the treatment of severe FH and outlines the recent advances in pharmacotherapies for this condition.*

87.•• Schwartz J, Winters JL, Padmanabhan A. Guidelines on the use of therapeutic apheresis in clinical practice-evidence-based approach from the Writing Committee of the American Society for Apheresis: the sixth special issue. J Clin Apher. 2013;28:145–284. *Latest guidelines on therapeutic apheresis of the American Society of Apheresis*.