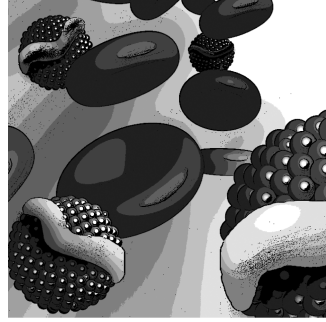

Current challenges in the management of patients with familial hypercholesterolemia

Familial hypercholesterolemia (FH) is a codominant monogenic disorder of lipoprotein metabolism, characterized by severely elevated levels of LDL cholesterol from birth onwards. Despite the availability of reliable diagnostic strategies, the vast majority of FH patients remain undiagnosed. Treatment of FH is mandatory to prevent premature cardiovascular disease and statins are the drug of choice. However, in some FH individuals, statins alone or in combination do not allow the attainment of therapeutic goals. LDL apheresis may be an option, mainly in homozygous FH. Nevertheless, the new lipid-lowering agents (blockers of apoB synthesis or PCSK9 inhibitors) hold promise for patients with resistant FH. There are still concerns when beginning pharmacological interventions in children with FH and also the management of FH in women of childbearing age or during pregnancy is a clinical dilemma. In the present article, these current challenges in the management of FH will be discussed.

KEYWORDS: apoB inhibitor ▪ children ▪ diagnosis ▪ familial hypercholesterolemia ▪ LDL receptor ▪ molecular genetics ▪ PCSK9 inhibitor ▪ pregnancy ▪ statins

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Familial hypercholesterolemia (FH) is an inherited disorder of lipid metabolism, very common in the clinical practice [1]. It causes high levels of LDL cholesterol (LDL-C), which leads to premature coronary heart disease (CHD). Early analyses have indicated that approximately half of men with FH, if untreated, will have developed clinically evident CHD by the age of 55 years, and one-third of women by the age of 60 years [2,3]. Even though a decline has been observed in the mortality rate associated with FH in the last 30 years [4], more recent investigations demonstrated that the event-free survival rate in untreated FH patients remain low (approximately 40% during a 12-year follow-up) [5], further confirming that this condition still carries a significantly increased risk of CHD. Despite FH being a life-threatening condition, the vast majority of affected individuals remain undiagnosed or are only diagnosed after their first coronary event [6,7]. Although it has been reported that a significant reduction in mortality and morbidity in FH can be achieved through the use of statins [6], in many patients the current treatments fail to reach the lipid targets [8]. The overall consequence is that too many FH individuals still experience a high CHD risk. In this review, we will examine the current major challenges in the management of patients with FH and the ways in which clinical approaches to this severe metabolic disorder can be improved.

Diagnosing FH

It is known that the FH phenotype is caused by mutations within three genes (*LDLR*, *APOB* and *PCSK9*) all regulating the metabolism of LDL particles [9]. Among these, mutations in the *LDLR* gene are the most frequent [9]. The *LDLR* gene is located on chromosome 19p13.2 and codes for a transmembrane glycoprotein that is expressed on the surface of most cells and is responsible for removing approximately two-thirds of LDL circulating in the plasma [1]. Therefore, defects in LDL receptor (LDLR) function are accompanied by slowed catabolism of LDL particles that results in the accumulation of LDL-C in the plasma [1].

FH is inherited as an autosomal dominant trait and appears early in life as two clinical forms: the heterozygous form (heFH), of which prevalence may range from 1:500 to 1:150 individuals in the general population [10], and the homozygous form (hoFH), which is rarer, being present in one in 1,000,000 individuals [1]. Typically, these two forms show distinct phenotypes, as plasma levels of total cholesterol in heFH are between 300 and 500 mg/dl, while those in hoFH are much higher (from 600 to 1200 mg/dl) [1]. However, hypercholesterolemia in FH is associated with a

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high degree of variability in the age of onset and severity. Indeed, a proportion of children who are carriers of a mutation causing FH may present initially with lipid levels within the normal range and elevated levels may develop only at a later age [11]. In addition to high cholesterol, FH patients may show tendon xanthomata (e.g., small modularity tendons of metacarpal–phalangeal joints), the presence of which must be considered as a pathognomonic sign of this disease [1]. Unfortunately, tendon xanthomata are present in only 30% of FH patients and, therefore, the lack of this sign does not certainly exclude the presence of FH.

From the above, we must recognize that there is no individual diagnostic test with sufficient specificity and sensitivity to reliably detect FH. Therefore, several international groups have developed diagnostic criteria based on a combination of clinical signs, family history and cholesterol measurements [12–14,101,102]. Recently, the European Society of Cardiology and the European Atherosclerosis Society guidelines have proposed criteria for the clinical diagnosis of heFH based on the Dutch point score system [15]. This score appears to perform better in the presence of tendon xanthomata [15]. Nevertheless, in most patients, a Dutch score above five gave an overall receiver-operating curve of 0.72 to correctly identify true FH [16].

Unfortunately, it has been reported that the simple use of clinical criteria to diagnose FH identifies only approximately 50–60% of affected individuals [17]. Due to the genetic nature of FH, the gold standard for making a definitive diagnosis should be the identification of the mutation in the *LDLR* gene. So far, more than 1000 different mutations have been found to cause FH [103]. They are of various types (missense, nonsense, small and large deletions or gene rearrangements) and located either in the coding (exons) or untranslated (introns) regions of the *LDLR* gene, including the promoter. Only a few mutations are found in seemingly unrelated families, but this probably occurs because of the 'founder effect' seen in very specific geographic areas, such as South Africa, Quebec, Canada and Lebanon, where the prevalence of FH is >1% of the general population [18].

As mentioned above, in addition to the *LDLR* gene, other genes have been involved in causing a hypercholesterolemic syndrome that resembles FH. In particular, it has been shown that some FH patients carry a mutation in a gene called *PCSK9* [19]. This gene, located on chromosome 1p32, is made up of 12 exons and encodes PCSK9, a protein of 692 amino acids. PCSK9 is mainly expressed in the liver and small intestine and has the ability to degrade the LDLR protein. Mutations leading to an increase in the proteolytic capacity (gain-of-function mutations) of PCSK9 cause accelerated destruction of LDLR and, therefore, a reduced availability of this protein on the cell surface [20]. As a consequence the catabolism of LDL is reduced and, thereby, an elevation of LDL-C concentration, which is of the same magnitude of that in heFH, develops. In addition, mutations in the *APOB* gene, which codes for apoB, the ligand for LDLR, may cause FH by impairing LDL to LDLR binding [21]. It has been estimated that this condition, also called familial defective apoB, is present in approximately 6% of FH cases and is associated with better drug responses and prognosis [21]. Overall, this gives FH an extreme variability from a molecular point of view. Nevertheless, in recent years, several methods have been developed for DNA-based rapid mutation screening, even though all have drawbacks either with regard to use of toxic chemicals, radiolabeling, sensitivity or specificity. More recently, the widespread use of direct DNA sequencing techniques may definitively facilitate the genetic diagnosis of FH, providing a good rate of mutation detection (~70–80%) in a relatively short time and at reasonable costs [22]. It has been suggested that the full sequencing of *LDLR*, *APOB* exon 26 and exon 7 of *PCSK9* is a reasonable strategy for the genetic diagnosis of FH [23]. However, when the mutation is known for a proband, DNA tests in relatives will give an unequivocal result within 1–2 days, so that other family members can be diagnosed quickly and cheaply.

One question remaining is whether genetic screening should be universal or limited to few well-selected individuals. Based upon the fact that case finding among relatives of FH cases (cascade screening) appears to be the most cost-effective strategy, while universal systematic screening the least cost-effective, several guidance reports have recommended molecular testing as a part of cascade screening [24–26,102]. In addition, it has been convincingly demonstrated that providing patients with a definite diagnosis of FH based upon genetic testing does not cause any adverse psychological consequences [27], but results in more patients being adequately treated. For example, it has been reported that 2 years after the molecular diagnosis of FH, the number of patients regularly taking lipid-lowering

medications increased by 50% [28]. Again, in 361 mutation carriers, there was a further 14% reduction in LDL-C levels 6 months after genetic testing and this was associated with a 53.0% reported change in drug therapy and the doubling in the number of individuals with total cholesterol below 200 mg/dl [26].

Despite the availability of reliable diagnostic criteria for FH, several surveys have demonstrated that they are not fully implemented in general clinical practice. For example, in a registry study carried out in Oxfordshire (UK), the overall prevalence of FH ascertained by Simon Broom criteria was 0.54/1000, which was well below the expected prevalence of approximately 2/1000 [29]. This figure indicates that only approximately a quarter of predicted cases of FH were diagnosed routinely, while the vast majority remained undiagnosed **(Figure 1)**. Moreover, the underdiagnoses were even greater among children and young adults: only two children aged under 10 years and 12 aged 10–19 years were identified. Although the situation might have been improved since the year 2000, the underdiagnosis of FH remains a global challenge, with correct identification ranging from less than 1% in Russia to 20% in The Netherlands and 44% in Iceland [6].

It is not known why patients with FH are often missed in primary care, but many seem to be diagnosed in middle age when family members present with CHD [29]. Although patients diagnosed with familial FH are instructed to contact their relatives, several studies have shown that this is not effective in practice [24]. The lack of national screening programs, the limited usefulness of clinical evaluation among children and young adults in whom clinical signs are rarely present and the low referral rate to specialists for cascade DNA testing all probably contribute. [30]. Despite all this, we have a duty to overcome these problems [31]. We need to implement in clinical practice the current guidelines for the management of FH and also ensure our local primary care trusts understand the number of life-years that can be cost effectively saved by cascade screening for FH and, therefore, fund the screening and DNA-based diagnosis of first-degree relatives of the index cases.

Reaching lipid goals in FH

Effective treatment is available to prevent early-onset heart disease for individuals with FH. This comprises the use of statins to reduce LDL-C levels combined with lifestyle changes, particularly smoking cessation. It has been demonstrated that monotherapy with high dosages of powerful statins may produce up to 50% reduction of LDL-C concentration in FH [32]. However, the benefit of these treatments on vascular outcomes has not been carefully determined as no randomized placebo-controlled clinical outcome trials of statin treatment have been conducted for ethical reasons. Nevertheless, useful information can be derived from large, long-term observational studies. For example, in a cohort study enrolling 1707 asymptomatic FH patients receiving statin therapy [5], the risk of CHD was reduced by 76% (hazard ratio: 0.24; 95% CI: 0.18–0.30; $p < 0.001$) over a mean follow-up of 8.5 years. Notably, the risk of myocardial infarction in these statin-treated patients was not significantly greater than that in an age-matched sample from the general population. Again, in a registry study involving 3382 FH patients (aged <80 years) [33], the CHD standardized mortality ratios (compared with the population in England and Wales) before and after 1 January 1992 (e.g., before and after the widespread use of statins) fell by 37% and this benefit was even greater in the younger groups (-76% in the 20–39-year-old age group). Primary prevention resulted in a 48% reduction in CHD mortality, with a smaller reduction of nearly 25% in patients with established disease. The coronary mortality was reduced more in women than in men. These data agree with findings from trials using carotid intima–medial thickness (IMT) as a surrogate cardiovascular outcome. In particular, the ASAP study, the largest randomized-controlled trial comparing the effect of 80 mg once daily (q.d.) atorvastatin

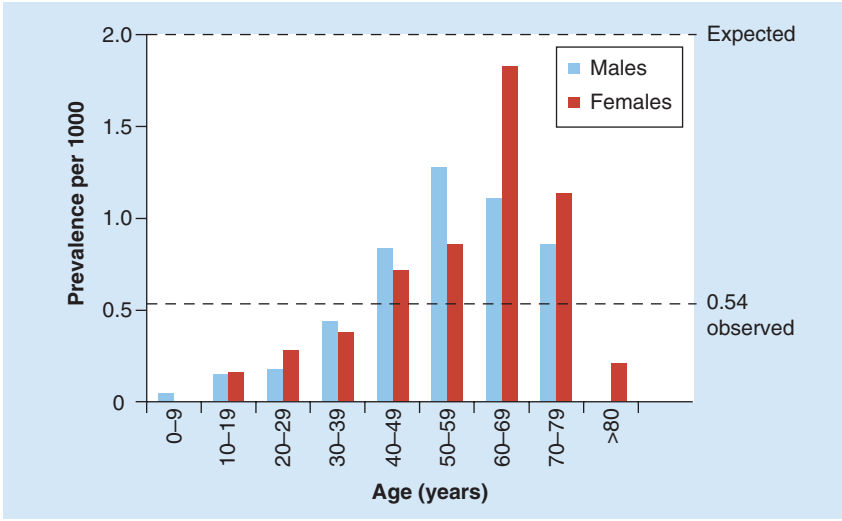

Figure 1. Age- and sex-specific prevalence of diagnosed cases of familial hypercholesterolemia among residents in Oxfordshire (UK).
Data taken from [29].

versus 40 mg q.d. of simvastatin on IMT changes, in 326 FH patients, demonstrated that the higher LDL-C reduction achieved in the atorvastatin-treated compared with the simvastatin-treated group (51 vs 41%) was associated after 2 years with a significant regression of carotid IMT (-0.031 vs +0.036 mm; $p < 0.001$) [34].

Largely based on extrapolation from surrogate outcome studies, all current guidelines strongly suggest treating FH aggressively and have indicated as a therapeutic target in these patients a LDL-C value of <100 mg/dl or, at least, 50% LDL-C reduction [15]. The reaching of this LDL-C target in FH is a challenge [35–37]. It becomes even more difficult (or impossible) if a heFH patient requires LDL-C of <70 mg/dl due to the presence of overt CHD or additional risk factors (e.g., diabetes and hypertension), or in the presence of hoFH. The use of high dosage of high-potency statins may be a practical option. Indeed, it has been reported that employing rosuvastatin at the dosage of 80 mg q.d., the percentage of heFH individuals reaching LDL-C goals was significantly higher than that obtained with atorvastatin at 80 mg q.d. (58 vs 44%; $p < 0.001$) [38]. The addition of other lipid-lowering compounds (especially ezetimibe, but also fibrates, and bile acid-binding resins) to high potency statins may be another possibility. For example, in a small trial involving 17 Japanese patients with heFH, the coadministration of rosuvastatin (20 mg q.d.), ezetimibe (10 mg q.d.) and granulated colestimide (3.62 g q.d.) resulted in a LDL-C reduction from an average of 296.6 to 100.1 mg/dl (-66.2%; $p < 0.001$), with 44% of patients achieving LDL-C of <100 mg/dl [39]. Despite this potential, there are no data demonstrating that either the addition of ezetimibe to high-dose statin [40] or any other combination is able to produce any further cardiovascular protection in FH.

An alternative treatment for severe refractory FH is represented by LDL apheresis. Several methods are now available for performing this procedure, of which a detailed description is out of the scope of the present review (see [41] for more details). Despite some differences, all of them are able to lower LDL-C and lipoprotein(a) efficiently and safely when performed weekly or bi-weekly. The benefit of LDL apheresis has been evaluated in seven angiographic studies involving FH patients (mainly heterozygotes), showing coronary artery disease (CAD). A recent analysis of their results in comparison with those obtained during dietary and drug trials indicated that FH patients treated with LDL apheresis showed less progression (18 vs 46%, and 33%) and more regression or no changes (82 vs 54%, and 67%) compared with those treated with other regimens [41]. Although the difference did not reach statistical significance, these trends suggest that LDL apheresis plus drug therapy is just as or possibly more effective at reducing progression of CAD in FH than drug therapy alone. Fewer studies have explored the effectiveness of LDL apheresis at reducing cardiovascular events in FH patients. In a nonrandomized trial, 43 FH patients were allocated to treatment with LDL apheresis plus drugs and 87 received drug therapy [42]. Over a period of 6 years, LDL-C decreased by 58% in the apheresis group and by 28% in the drug group. The incidence of coronary events during the trial was 70% lower in patients treated with LDL apheresis plus drugs than in those on drugs alone ($p < 0.01$). There is a large consensus that LDL apheresis should be the treatment of choice in all hoFH patients from the age of 7 years onwards unless their serum cholesterol can be reduced by >50%, and in heFH patients whose coronary disease progresses, as well as in those whose LDL-C remains >200 mg/dl or is decreased by <40% with maximal drug therapy [41].

New cholesterol-lowering drugs in the management of FH

Several new cholesterol-lowering drugs under investigation might be proven to be useful in ameliorating FH treatment. These new compounds can be classified into two groups: those aimed at reducing the liver production of VLDL and those aimed at further stimulating the availability of LDLR, mainly in the liver cells.

The rationale for the first approach relies on the fact that several *in vivo* lipoprotein turnover studies have demonstrated that the lack (or the reduced function) of LDLR not only causes an impaired receptor-dependent clearance of circulating LDL, but is also associated with increased production of VLDL by the liver [43]. As VLDLs are the metabolic precursors of LDL, the inhibition of VLDL synthesis and secretion might further help in reducing LDL-C levels, particularly in those FH patients showing severely impaired (or absent) LDLR activity, such as in hoFH individuals. The major factor regulating VLDL assembly and secretion is the availability of apoB100, the typical apolipoprotein of LDL [44]. The inhibition of its synthesis has been demonstrated to markedly reduce VLDL secretion by the liver [44].

Mipomersen (ISIS 301012; Isis Pharmaceuticals, CA, USA and Sanofi-Genzyme Pharmaceutical, MA, USA) is a 20-mer oligonucleotide (2′-*O*-[2-methoxy]ethyl-modified oligonucleotide), a second-generation antisense oligonucleotide, complementary to the coding region for human-specific apoB100 mRNA. It acts by binding to apoB100 mRNA, thus targeting it towards destruction [45]. This drug has been tested in a number of trials **(Table 1)**. A total of 51 hoFH patients on maximally tolerated lipid-lowering therapy were treated with 200 mg/week of mipomersen or placebo. The mean percentage change in LDL-C was significantly greater with mipomersen (-24.7%; 95% CI: -31.6 to -17.7) than with placebo (-3.3%; CI: -12.1 to 5.5; p < 0.001) [46]. However, the response to mipomersen was highly variable, with some patients achieving a reduction in LDL-C of 50–80%, whereas others failed to respond. The most common adverse events associated with mipomersen use were injection-site reactions, resulting in two patients discontinuing therapy. A total of 12% (four out of 34) of patients in the mipomersen group, compared with none in the placebo group, had an increase in the concentrations of alanine aminotransferase (ALT; ≥three-times the upper limit of normal [ULN]).

The safety and effects of this medication have also been evaluated in subjects with severe heFH. A randomized, double-blind, placebo-controlled, dose-escalation study involving 44 patients with heFH received conventional therapy at the maximum tolerated doses [47]. Patients were randomized into four groups, with doses ranging from 50 to 300 mg/week during a 6-week treatment period. Patients assigned to the 300-mg dose continued for an additional 7 weeks with once-per-week dosing. After 6 weeks of treatment, the LDL-C level was reduced by 21% from baseline in the 200 mg/week dose group (p < 0.05) and 34% from baseline in the 300 mg/week dose group (p < 0.01), with a concomitant reduction in apoB of 23% (p < 0.05) and 33% (p < 0.01), respectively. Injection-site reactions were the most common adverse event. Elevations in liver transaminase levels (>three-times ULN) occurred in four (11%) of 36 patients assigned to active treatment; three of these patients were in the highest dose group. The most recent study on mipomersen involved 124 heFH patients with CAD demonstrating LDL-C of >100 mg/dl on the maximally tolerated statin dose [48]. They were randomized to a weekly subcutaneous dose of 200 mg mipomersen or placebo (2:1) for 26 weeks. Of the randomized patients, 114 (41 placebo, 73 mipomersen) completed the treatment. Mean LDL-C decreased significantly with mipomersen (-28.0%; 95% CI: -34.0 to -22.1%) compared with a 5.2% (95% CI: -0.5 to 10.9%) increase with placebo; p < 0.001). Mipomersen significantly reduced apoB (-26.3%), total cholesterol (-19.4%), and lipoprotein(a) (-21.1%) compared with placebo (all p < 0.001). Five mipomersen patients (6%) had two consecutive ALT values of >three-times ULN, at least 7 days apart. Hepatic fat content increased by a median of 4.9% with mipomersen versus 0.4% with placebo (p < 0.001) [48].

The potential impact of mipomersen on intrahepatic triglyceride (IHTG) content in FH has been specifically evaluated in a randomized, double-blind, placebo-controlled study [49]. A total of 21 patients with heFH received a weekly subcutaneous dose of 200 mg mipomersen or placebo for 13 weeks, while continuing conventional lipid-lowering therapy. The change in IHTG content from week 0 to 15 was measured by proton magnetic resonance spectroscopy. As expected, mipomersen administration showed a significant cholesterol-lowering effect as after 13 weeks LDL-C was reduced by 22.0% and apoB by 19.9% (both p < 0.01). A nonstatistically significant trend towards an increase in IHTG content was seen in mipomersen-treated FH patients (placebo: baseline: 1.2% and week 15: 1.1%, change -0.1 [standard deviation: 0.9]; mipomersen: baseline: 1.2% and week 15: 2.1%, change 0.8 [standard deviation: 1.7]; p = 0.0513). However, only one patient developed a mild steatosis (IHTG above 5.6%) and none showed clinically significant increases in ALT (>three-times ULN) or other measures of liver function. However, the relatively short-term duration of this trial precludes the possibility of any definitive conclusion about this potential side effect of inhibition of apoB synthesis.

Another way to inhibit VLDL synthesis is to reduce the incorporation of lipids into nascent VLDL lipoprotein; a good target could be MTP, which, within liver cells, couples triglycerides to the lipid-poor apoB100, allowing the formation of nascent lipoprotein [50]. Lomitapide (AEGR-733, Aegerion Pharmaceuticals, Inc., MA, USA) is a MTP inhibitor, which has been demonstrated to be able to block VLDL lipoprotein assembly and secretion in the liver **(Table 1)**. In the first Phase II trial, lomitapide was employed in the treatment of six hoFH patients at four different dose regimens (0.03, 0.1, 0.3 and 1.0 mg/kg of

Table 1. Summary of LDL cholesterol-lowering effects of new drugs in patients with familial hypercholesterolemia.

Study	Patient population	Duration	Dosage	Baseline LDL-C (mg/dl)	LDL-C (% change)	Major side effects	Ref.
Mipomersen							
Raal *et al.* (2010)	hoFH (n = 51)	26 weeks	Placebo 200 mg/week	401.4 ± 142.8 440.0 ± 139.0	-3.3 -25	Injection-site reactions, 12% increase of ALT	[46]
Akdim *et al.* (2010)	heFH (n = 44)	6 weeks	Placebo 50 mg/week 100 mg/week 200 mg/week 300 mg/week	170.6 ± 46.3 206.5 ± 77.2 173.7 ± 38.6 163.7 ± 30.9 173.7 ± 34.7	0 -13 -11 -21 -34	Injection-site reactions, 17% increase of liver transaminases†	[47]
Visser *et al.* (2010)	heFH (n = 21)	13 weeks	Placebo 200 mg/week	155 ± 31 155 ± 37	1.0 -22	Injection-site reactions, flu-like illness, 10% with mild steatosis	[49]
Stein *et al.* (2012)	heFH (n = 124)	26 weeks	Placebo 200 mg/week	142.8 152.8	5 -28	6% of patients with mipomersen had ALT increase; hepatic fat content increased by 4.9% with mipomersen vs 0.4% with placebo	[48]
Tardif *et al.* (abstract; 2011)	Severe heFH (n = 58)	26 weeks	Placebo 200 mg/week	248.6 275.6	13 -36		[78]
Lomitapide							
Cuchel *et al.* (2007)	hoFH (n = 6)	4 weeks	1 mg/kg/day	614.1	-50.9	Increased stool frequency, 60% increase liver transaminase†, hepatic steatosis	[51]
Cuchel *et al.* (2013)	hoFH (n = 29)	26 weeks	40 mg/day (median dose)	335.8 ± 111.9	-50.0	Gastrointestinal symptoms, 34% increase in liver transaminase†, increase in hepatic fat (from 1 to 8%)	[52]
PCSK9 inhibitors							
Stein *et al.* (2012)	heFH (n = 21)	57 days	Placebo 50 mg/every 3 weeks 100 mg/every 3 weeks 150 mg/every 3 weeks	133.2 ± 20.7 125.0 ± 12.1 135.8 ± 41.1 140.2 ± 26.2	 -31.4 -57.6 -55.7	13% increase in CPK (>three-times ULN) but also in those taking atorvastatin	[55]
Stein *et al.* (2012)	heFH (n = 77)	12 weeks	Placebo 150 mg/every 4 weeks 200 mg/every 4 weeks 300 mg/every 4 weeks 150 mg/every 2 weeks	150.0 ± 34.0 166.7 ± 50.2 169.8 ± 56.7 139.7 ± 24.7 147.1 ± 32.4	-10.6 -28.9 -31.5 -42.5 -67.9	Injection-site reactions, infections, gastrointestinal disorders; no changes in liver or muscle enzymes	[56]
Raal *et al.*	heFH (n = 167)	12 weeks	Placebo 350 mg/every 4 weeks 420 mg/every 4 weeks	162.1 ± 42.5 158.3 ± 46.3 150.5 ± 34.7	1.1 -42.7 -55.2	Injection site pain, skin burning, headache, 3% increase CPK (>five-times ULN) and 1.8% increase in liver enzymes	[57]

†*Increase of liver transaminases indicates >three-times ULN.*
ALT: Alanine aminotransferase; CPK: Creatine phosphokinase; heFH: Heterozygous familial hypercholesterolemia; hoFH: Homozygous familial hypercholesterolemia; LDL-C: LDL cholesterol; ULN: Upper limit of normal.

bodyweight per day). It has been observed that the highest dose (1.0 mg/kg) reduced LDL-C levels and apoB levels by 50.9 and 55.6%, respectively, from baseline, after 4 weeks of treatment ($p < 0.001$ for both comparisons) [51]. Adverse events included elevation of liver aminotransferase levels and gastrointestinal side effects, particularly increased stool frequency and marked accumulation of hepatic fat, which at the highest dose ranged from <10 to >40%.

In a more recent, single-arm, open-label, Phase III trial in hoFH, lomitapide was administered to 29 patients (aged >18 years) at a dosage increasing from 5 mg to a maximum of 60 mg q.d. on the basis of safety and tolerability [52]. Although the primary end point of this trial was the mean percentage change in LDL-C levels from baseline to week 26, patients remained on lomitapide through to week 78 for the safety assessment. A total of 23 enrolled patients completed both the efficacy phase and the full study. At the end of 26 weeks of treatment, the median dose of lomitapide was 40 mg q.d. and LDL-C was reduced by 50% (95% CI: -62 to -39; $p < 0.0001$); plasma levels of LDL-C were <100 mg/dl in eight patients (35%). A slightly decreased lowering effect was seen over time as LDL-C remained reduced by 44% (95% CI: -57 to -31; $p < 0.0001$) at week 58 and 38% (-52 to -24; $p < 0.0001$) at week 78. Although gastrointestinal symptoms were the most common side effects, no patients discontinued the treatment because of liver abnormalities. Four patients (15%) had aminotransferase levels of >five-times ULN, but this resolved after dose reduction or temporary interruption of lomitapide. In this trial, no data on change in liver fat content were reported.

Other potential therapies to further reduce LDL-C in FH include PCSK9 inhibitors. As indicated above, PCSK9 is a serine protease that binds to the LDLR, promoting its degradation, thereby regulating LDL metabolism. The action of these drugs is to block the function of wild-type PCSK9, thus allowing more LDLR proteins available to remove circulating LDL particles. Preliminary results of PCSK9 inhibitors (antisense and monoclonal antibodies) in nonhuman primates demonstrate 50–70% reductions in circulating LDL that were transient with the antibody inhibitor [53,54].

Recently, a number of trials evaluating the potential benefit of two different PSCK9 inhibitors in the treatment of FH have been published **(Table 1)**. In the first small study, the efficacy and safety of the anti-PCSK9 monoclonal antibody REGN727 (Regeneron, NY, USA) was tested in a small group of 21 patients with heFH who were receiving atorvastatin (baseline LDL-C of >100 mg/dl) [55]. REGN727 at doses of 50, 100 or 150 mg were administered subcutaneously on days 1, 29 and 43. At baseline, LDL-C concentrations ranged from 125 to 140 mg/dl in the different dosing groups. On day 57, the doses of 50, 100 and 150 mg reduced measured LDL-C levels to 80.6, 60.0 and 65.4 mg/dl, respectively, for a difference in the change from baseline of -41.4, -57.6 and -55.7%, respectively, compared with placebo ($p < 0.001$ for all comparisons). Stein *et al.* assessed the REGN727 inhibitor in a larger, multicenter, randomized, placebo-controlled Phase II trial [56]. A total of 77 heFH patients presenting with LDL-C of >100 mg/dl during statin and/or ezetimibe treatment were randomly assigned to receive REGN727 150, 200 or 300 mg every 4 weeks, or 150 mg every 2 weeks, or placebo every 2 weeks (ratio 1:1:1:1:1). Randomization was stratified by concomitant use of ezetimibe at baseline. LDL-C reduction from baseline to week 12 was 28.9% for 150 mg every 4 weeks ($p = 0.0113$), 31.5% for 200 mg every 4 weeks ($p = 0.0035$), 42.5% for 300 mg every 4 weeks ($p < 0.0001$) and 67.9% for 150 mg every 2 weeks ($p < 0.0001$), compared with 10.6% for placebo. One serious adverse event was reported with placebo and none with REGN727. No increases of >three-times ULN were reported for hepatic transaminases or creatine kinase. The most common adverse event was a 13% increase in creatine phosphokinase with one patient in the 300-mg REGN727 group terminating treatment.

A Phase II, multicenter, double-blind, randomized, placebo-controlled, dose-ranging study evaluated the efficacy and safety of AMG 145 (Amgen, CA, USA), another human monoclonal antibody against PCSK9 in heFH patients [57]. Patients diagnosed by Simon Broome criteria were selected on the basis of having LDL-C ≥100 mg/dl despite statin therapy with or without ezetimibe. A total of 168 were randomized (1:1:1) to receive 350 or 420 mg of AMG 145, or placebo, subcutaneously every 4 weeks. After 12 weeks of treatment, LDL-C reduction was 43 and 55% with AMG 145 350 and 420 mg, respectively, compared with a 1% increase with placebo ($p < 0.001$ for both dose groups). Most (95%) patients on AMG 145 experienced reductions in LDL-C of at least 15% and 52% had reductions of 50% or more. Four patients in

the AMG 145 350-mg group and one patient in the 420-mg group were considered poor responders based on <15% reduction in LDL-C at week 12. The three most common treatment-related adverse events for AMG 145 (350 mg, 420 mg and placebo) were injection-site pain (7.3%; 3.6%; 1.8%), headache (5.5%; 1.8%; 0.0%) and skin burning sensation (1.8%, 3.6%; 0.0%). Three patients (one AMG 145 350 mg, one AMG 145 420 mg and one placebo) experienced adverse events that led to the discontinuation of treatment. Three patients experienced creatine phosphokinase (>five-times ULN) and two patients transaminase (>three-times ULN) elevation.

The results reported above clearly indicate that, in patients with established FH, strategies aimed at inhibiting VLDL synthesis or at blocking PCSK9 have the potential to increase the fall in LDL-C by more than 50% when prescribed in combination with standard lipid-lowering drugs. Although the inhibition of PCSK9 appears to have minimal adverse events and good tolerability, no long-term safety data are reported; moreover, concern still exists regarding the potential long-term consequences of increased liver fat in association with mipomersen or lomitapide treatment. In addition, the significance of patients' discomfort due to injection-site reactions or the possibility of developing neutralizing antibodies during treatment remain aspects that need to be carefully evaluated in future larger trials. Finally, a more accurate definition of those patients who might benefit most from these new drugs (hoFH, resistant heFH or FH individuals with concomitant CHD) still remains an open question. Nevertheless, the future years appear very promising in offering new therapeutic approaches aimed at improving lipid control in FH patients.

Treating FH in children & during pregnancy

As FH starts early in life and is associated with a dramatically increased risk of CHD in the young, a reasonable approach should be to treat FH as soon as possible, even during childhood. However, the treatment of FH children with statins is still a challenge. Several trials have been carried out in children and all definitively demonstrated that statin therapy effectively lowered LDL-C levels in FH children, and LDL-C levels were reduced by approximately 30% (ranging from 23 to 50%) [58,59]. Importantly, statin therapy was not associated with clinically significant changes in measures of growth or maturation, liver enzymes, serum creatine kinase or incidence of myopathy. However, when treating children pharmacologically, particularly when the treatment regards a life-long condition such as FH, considerations must be made about potential long-term side effects. As the durations of controlled statin trials involving FH children have been rather short, lasting a maximum of approximately 2 years, it was not possible to make any definite statements regarding the safety of long-term statin treatment in FH children. In an uncontrolled study, which is actually the longest follow-up study of FH children on statin therapy, 186 children (aged 8–18 years) were treated with pravastatin for an average of 4.5 years (2.1–7.4 years) and no serious adverse events were reported [60].

Due to the lack of sound clinical evidence, opinions regarding the age at which statin therapy should be initiated in FH children vary **(Table 2)**. However, with little differences, many agree that the ages of 8–10 years is a reasonable time to decide starting pharmacological therapy in these children [61–66,104,105]. Are there sources of scientific evidence to support these recommendations? In trying to answer this difficult question, it might be relevant to identify at what age the accumulation of LDL particles start to produce significant and premature vascular changes in children with FH. The only way to approach this problem is to use surrogate markers of atherosclerosis, such as the thickening of the carotid IMT. This measure can be obtained accurately in children and changes over time can be monitored [67]. Studies from The Netherlands have shown clearly that the carotid IMT of FH children aged 8–19 years was significantly greater than in their unaffected siblings [68], strongly suggesting that the actual atherosclerotic disease process must be already ongoing at an early age. It is well known that atherosclerotic complications due to FH are strongly related to duration of exposure to increased LDL-C, the so-called 'LDL-C burden', which can be calculated by the sum of LDL-C levels multiplied by the years of age [69]. In a very recent position paper about statin treatment in FH children, it has been estimated that a non-FH adult may show a LDL-C burden of 6.17 g by the age of 55 years, while the same LDL-C burden can be reached by the age of 35 years in untreated FH patients [70]. If the patient is treated since the age of 18 years, this exposure level will be delayed to the age of 48 years and it will be further delayed to the age

Table 2. Summary of current recommendations for treating familial hypercholesterolemia children with statins.

Guidelines	Recommendations	Ref.
NICE and Scottish Intercollegiate Guidelines Network	Use statins from the age of 10 to 12 years	[104,105]
National Lipid Association Expert Panel	Consider statins over 8 years of age	[61]
American Academy of Pediatrics	Use statins over 8 years of age if LDL cholesterol is >190 mg/dl	[62]
Avis *et al.*	Consider statin therapy from the age of 8 years	[63]
Australasian Guidelines	Consider statin therapy after the age of 10 years also considering the presence of other risk factors; evaluate the familial cardiovascular risk	[64]
Belgian Consensus Panel	Consider statin therapy at the age of 10–14 years if LDL cholesterol is >150 mg/dl despite diet and if other risk factors are present; between the age of 14–18 years eventually increase dosages to achieve LDL cholesterol of <130 mg/dl	[65]
American Heart Association Atherosclerosis, Hypertension and Obesity Youth Committee	Consider statins after 10 years of age; in girls after the onset of menses	[66]

of 53 years if the patient has been treated since the age of 10 years.

Although these calculations make some assumptions that can produce an underestimate of the actual LDL-C-related risk (e.g., children with more severe heFH may have higher LDL-C exposure or FH children with family history of CHD might be more prone to developing atherosclerosis), they may represent a rationale for suggesting the initiation of statin therapy in FH children within the 8–10 years age range. This approach can be further supported by the results of placebo-controlled trials that demonstrated that the use of statins in children with FH significantly reduces progression to thicker carotid IMT over 2 years compared with non-treated children with FH [71], again proving the clinical utility of early commencement of statins in children with FH.

Based on this reasoning, we fully agree that in deciding to prescribe statins to a FH child [70], clinicians should consider the following: there is no rationale for starting statin therapy in FH children before the age of 8 years; statin treatment should be started by the age of 10 years unless important contraindications are present (e.g., other severe disease or risk of myopathy); and statin treatment could be delayed only if the disease phenotype is mild (i.e., serum LDL-C level is below 150 mg/day after dietary intervention and no severe family history or several additional CAD risk factors are present).

There is no doubt that the battle against FH will rely most on the early treatment of this condition. We hope that future long-term follow-up studies in children will show the advantages, as well as highlight any possible long-term side effects, of early-onset long-duration statin treatment. This will generate information that can be useful in the development of effective programs for managing FH children in clinical practice.

Physicians are faced with a treatment dilemma if a FH female presents either with an established pregnancy or a wish for pregnancy, since all systemically absorbed lipid-lowering medication are contraindicated during pregnancy in order to avoid potential teratogenic effects in the unborn child [72]. In considering this challenge, several aspects have to be considered. It is known that in normal women, pregnancy is associated with a 30–50% increase of LDL-C as a result of enhanced cholesterol synthesis in the liver. Unfortunately, few studies have investigated the changes in LDL-C during pregnancy in FH women. A Scandinavian group analyzed lipid profiles between week 17 and 36 of gestation in 22 FH patients in comparison with 149 normocholesterolemic individuals [73]. Although the percent increase in cholesterol levels was equal between the two groups, the absolute increase (LDL-C: 73.5 vs 31 mg/dl, respectively) was more pronounced in the FH group due to elevated levels at baseline. It is unknown whether such an increase in cholesterol levels during pregnancy will lead to enhanced atherosclerosis for the FH mother. Nevertheless, taking into account that in a pregnant FH women, the total 'unprotected' period should consist of at least 12–15 months and that the achieved cholesterol levels exceed approximately threefold the physiological range, the growth of an atheroma is not unlikely. There are no reports indicating lipotoxicity of high maternal cholesterol levels for the fetus, but it is has been suggested that maternal hypercholesterolemia could induce increased cardiovascular risk for offspring [74–76].

All together these considerations prompted the development of a strategy to manage FH women of childbearing age or during pregnancy mainly based on the *primum non nocere* principle [76]. In short, even though available reports in humans do not show adverse safety signals, when lipid-lowering medication is first considered for females of childbearing age, the risks to the pregnancy and the fetus should be carefully discussed. Women wishing to become pregnant should be advised to stop use of statins 3 months prior to attempting to conceive. In the case in which a drug treatment is necessary, one option could be to use bile acid resins or other poorly absorbable drugs (e.g., colestyramine and colesevelam). Although FH women who experience an unplanned pregnancy while taking statins should be reassured that the chance of an adverse pregnancy outcome is minor [77], they must be advised to stop treatment immediately and be referred to an obstetrician for fetal assessment.

In light of the lack of evidence-based support for much of this advice, teratogenicity of statins and other lipid-lowering medications should be further investigated. In addition, large follow-up studies are needed to determine the effect of hypercholesterolemia during pregnancy on CVD risk for FH women, as well as for their offspring.

Conclusion

Several years of clinical and genetic investigations provided reliable diagnostic criteria for FH. Unfortunately, these criteria are not fully implemented in routine clinical practice and many FH patients still receive diagnosis only after an ischemic event. The lack of national screening programs, the limited usefulness of clinical evaluation among children and young adults and the low referral rate to specialists for cascade DNA testing all probably contribute to this limitation. The treatment of FH using currently available drugs is still a challenge due to the fact that in some patients it is very difficult to reach the lipid targets. The identification of new targets to control LDL levels and the development of appropriate drugs might allow overcoming these difficulties. Despite uncertainties on pharmacological therapy in FH children, there is rationale for proposing statin treatments after the age of 8 years, unless the disease phenotype is very mild and no additional risk factors are present. It is conceivable not to use statins during pregnancy or lactation in FH women. However, those who experienced an unplanned pregnancy while taking stains should be reassured about the risk of adverse pregnancy outcomes. Alternative drugs should be used during pregnancy in these patients to reduce the time of exposure to very high LDL.

Executive summary

Diagnosis of familial hypercholesterolemia

- Familial hypercholesterolemia (FH) is a common, life-threatening genetic disorder of lipid metabolism. It is genetically heterogeneous as the underlying molecular defect can be detected in one of three genes (*LDLR*, *APOB* and *PCSK9*).
- FH is characterized by marked elevation of LDL cholesterol (LDL-C) caused by delayed clearance of circulating LDL particles.
- There is no single clinical criterion to make an unequivocal diagnosis of FH, but the combination of measurements of LDL-C, identification of family history of hypercholesterolemia and recognition of the presence of tendon xanthomata allow the diagnosis of FH in most of patients.
- The sequencing of the entire *LDLR* gene, of exon 26 of *APOB* gene and of exon 7 of *PCSK9* is the suggested strategy for genetic testing in suspected FH. With this method, up to 80% of cases can be accurately diagnosed. When the mutation is known for the proband, other family members can be genotyped quickly and cheaply.
- The implementation of cascade screening within affected families, as well as the promotion of national screening programs, might help to reduce the number of undiagnosed FH individuals within the population.

Treatment of FH

- Statins are effective in lowering LDL-C and cardiovascular risk in FH. All current guidelines strongly suggest treating FH aggressively and have indicated a therapeutic target in these patients of LDL-C levels of <100 mg/dl or, at least, a 50% LDL-C reduction.
- Stains alone or in combination allow the attainment of therapeutic goals in only 40–60% of FH patients. The new lipid-lowering agents (blockers of apoB synthesis or PCSK9 inhibitors) hold promise as an adjunct therapy in patients with resistant FH. However, the long-term efficacy and safety of these drugs need to be further demonstrated.

FH in children & during pregnancy

- There is evidence that an early therapeutic intervention significantly improves outcomes in FH patients. There is a general consensus that ages 8–10 years is a reasonable time to start pharmacological therapy in these children.
- Although it is safe to stop statins during pregnancy and lactation, FH women who experience an unplanned pregnancy while taking statins should be reassured that the chance of an adverse pregnancy outcome is minor.
- If necessary, the use of bile acid resins is a therapeutic option during pregnancy or lactation.

Future perspective

The diagnosis, definition and validation of a work f ow for cascade screening in patients with FH would require additional efforts. In addition, doctors need to implement in clinical practice the current guidelines for the management of FH and also to ensure health authorities understand the number of life years that can be cost effectively saved by early diagnosis of FH, and therefore fund the screening and DNA-based diagnosis of the first-degree relatives of the index cases. A careful evaluation of advantages and disadvantages of new LDL-lowering drugs will need to be carried out in future larger trials. Also, the definition of those patients who might benefit most from these new drugs should be pursued. Finally, future studies should evaluate the benefit of starting pharmacological therapy in young FH individuals, as well as large follow-up studies being needed to determine the effect on CVD risk of hypercholesterolaemia during pregnancy in FH mothers and their offspring.

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References

Papers of special note have been highlighted as:
▪▪ of considerable interest

1 Goldstein JL, Hobbs HH, Brown MS. Familial hypercholesterolemia. In: *The Metabolic and Molecular Bases of Inherited Disease.* Scriver CR, Beaudet AL, Sly WS *et al.* (Eds). McGraw-Hill, NY, USA, 2863–2913 (2001).

2 Slack J. Risks of ischaemic heart-disease in familial hyperlipoproteinaemic states. *Lancet* 1380–1382 (1969).

3 Stone NJ, Levy RI, Fredrickson DS, Verter J. Coronary artery disease in 116 kindred with familial type II hyperlipoproteinemia. *Circulation* 49, 476–488 (1974).

4 Sijbrands EJ, Westendorp RG, Defesche JC, de Meier PH, Smelt AH, Kastelein JJ. Mortality over two centuries in large pedigree with familial hypercholesterolaemia: family tree mortality study. *BMJ* 322, 1019–1023 (2001).

5 Versmissen J, Oosterveer DM, Yazdanpanah M *et al.* Efficacy of statins in familial hypercholesterolaemia: a long term cohort study. *BMJ* 337, a2423 (2008).

▪▪ **One of the best descriptions of the effectiveness of statins in patients with familial hypercholesterolemia (FH).**

6 Marks D, Thorogood M, Neil HA, Humphries SE. A review on the diagnosis, natural history, and treatment of familial hypercholesterolaemia. *Atherosclerosis* 168, 1–14 (2003).

7 Scientific Steering Committee on behalf of the Simon Broome Register Group. Mortality in treated heterozygous familial hypercholesterolaemia: implications for clinical management. *Atherosclerosis* 142, 105–112 (1999).

8 Sjouke B, Kusters DM, Kastelein JJP, Hovingh GK. Familial hypercholesterolemia: present and future management. *Curr. Cardiol. Rep.* 13, 527–536 (2011).

9 Rader DJ, Cohen J, Hobbs HH. Monogenic hypercholesterolemia: new insights in pathogenesis and treatment. *J. Clin. Invest.* 111, 1795–1803 (2003).

10 Benn M, Watts GF, Tybjaerg-Hansen A, Nordestgaard BG. Familial hypercholesterolemia in the Danish general population: prevalence, coronary artery disease, and cholesterol-lowering medication. *J. Clin. Endocrin. Metab.* 97, 3956–3964 (2012).

▪▪ **The authors estimated the prevalence of FH in a large population by applying the Dutch lipid clinic criteria in combination with molecular screening of most common Danish causative mutations. They demonstrated that the prevalence of FH may be higher than expected.**

11 Kessling AM, Seed M, Taylor R, Wynn V, Humphries SE. Rising cholesterol levels in children with familial hypercholesterolaemia. *Biomed. Pharmacother.* 44, 373–379 (1990).

12 Scientific Steering Committee on behalf of the Simon Broome Register Group. Risk of fatal coronary heart disease in familial hypercholesterolaemia. *BMJ* 303, 893–896 (1991).

13 Williams RR, Hunt SC, Schumacher C *et al.* Diagnosing heterozygous familial hypercholesterolemia using new practical criteria validated by molecular genetics. *Am. J. Cardiol.* 72, 171–176 (1993).

14 Goldberg AC, Hopkins PN, Toth PP *et al.* Familial hypercholesterolemia: screening, diagnosis and management of pediatric and adult patients: clinical guidance from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. *J. Clin. Lipidol.* 5(Suppl. 3), S1–S8 (2011).

15 Reiner Z, Catapano AL, De Backer G *et al.* ESC/EAS Guidelines for the management of dyslipidaemias. The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). *Eur. Heart J.* 32, 1769–1818 (2011).

16 Clarke RE, Padayachee ST, Preston R *et al.* Effectiveness of alternative strategies to define index case phenotypes to aid genetic diagnosis of familial hypercholesterolaemia. *Heart* 99, 175–180 (2013).

17 Lambert H, Humphries SE, Neil HA. Screening for hypercholesterolemia versus case finding for familial hypercholesterolaemia: systematic review and cost effectiveness analysis. *Health Technol. Assess.* 4, 1–123 (2000).

18 Betard C, Kessling AM, Roy M *et al.* Molecular genetic evidence for a founder effect in familial hypercholesterolemia among French Canadians. *Hum. Genet.* 88, 529–536 (1992).

19 Abifadel M, Varret M, Rabes JP *et al.* Mutations in *PCSK9* cause autosomal dominant hypercholesterolemia. *Nat. Genet.* 2, 154–156 (2003).

20 Benjannet S, Rhainds D, Essalmani R *et al.* NARC:1/PCSK9 and its natural mutants: zymogen cleavage and effects on the low density lipoprotein (LDL) receptor and LDL cholesterol. *J. Biol. Chem.* 47, 48865–48875 (2004).

21 Marduel M, Carrié A, Sassolas A *et al.* Molecular spectrum of autosomal dominant hypercholesterolemia in France. *Hum. Mutat.* 31, e1811–e1824 (2010).

22 Marks D, Wonderling D, Thorogood M *et al.* Cost effectiveness analysis of different

approaches of screening for familial hypercholesterolaemia. *BMJ* 324, 1303–1308 (2002).

23 Sharma P, Boyers D, Boachie C *et al.* Elucigene FH20 and LIPOchip for the diagnosis of familial hypercholesterolaemia: a systematic review and economic evaluation. *Health Technol. Assess.* 16, 1–266 (2012).

24 Marks D, Thorogood M, Neil SM, Humphries SE, Neil HAW. Cascade screening for familial hypercholesterolaemia: implications of a pilot study for national screening programs. *J. Med. Screen* 13, 156–159 (2006).

25 Umans-Eckenhausen MA, Defesche JC, Sijbrands EJ *et al.* Review of first 5 years of screening for familial hypercholesterolaemia in The Netherlands. *Lancet* 357, 165–168 (2001).

▪▪ **Reports the results of a national program dedicated to the identification of FH.**

26 Leren TP, Finborud TH, Manshaus TE, Ose L, Berge KE. Diagnosis of familial hypercholesterolemia ingeneral practice using clinical diagnostic criteriaor genetic testing as part of cascade geneticscreening. *Community Genet.* 11, 26–35 (2008).

27 Marteau T, Senior V, Humphries SE *et al.* Psychological impact of genetic testing for familial hypercholesterolemia within a previously aware population: a randomized controlled trial. *Am. J. Med. Genet. A* 128A, 285–293 (2004).

28 Huijgen R, Kindt I, Verhoeven SB *et al.* Two years after molecular diagnosis of familial hypercholesterolemia: majority on cholesterol-lowering treatment but a minority reaches treatment goal. *PLoS ONE* 5, e9220 (2010).

29 Neil HA, Hammond T, Huxley R *et al.* Extent of underdiagnosis of familial hypercholesterolaemia in routine practice: prospective registry study. *BMJ* 321, 148 (2000).

30 Qureshi N, Humphries SE, Seed M, Rowlands P, Minhas R. Identification and management of familial hypercholesterolaemia: what does it mean to primary care? *Br. J. Gen. Pract.* 59, 773–776 (2009).

31 Mant D. Commentary: what's so special about familial hypercholesterolaemia? *Br. J. Gen. Pract.* 59, 777–778 (2009).

32 Jones PH, Davidson MH, Stein EA *et al.* Comparison of the efficacy and safety of rosuvastatin versus atorvastatin, simvastatin, and pravastatin across doses (STELLAR* Trial). *Am. J. Cardiol.* 92, 152–160 (2003).

33 Neil A, Cooper J, Betteridge J *et al.* Reductions in all-cause, cancer, and coronary mortality in statin-treated patients with heterozygous familial hypercholesterolaemia: a prospective registry study. *Eur. Heart J.* 29, 2625–2633 (2008).

34 Smilde TJ, van Wissen S, Wollersheim H *et al.* Effect of aggressive versus conventional lipid lowering on atherosclerosis progression in familial hypercholesterolemia (ASAP): a prospective, randomized, double-blind trial. *Lancet* 357, 577–581 (2001).

35 Pijlman AH, Huijgen R, Verhagen SN *et al.* Evaluation of cholesterol lowering treatment of patients with familial hypercholesterolemia: a large cross-sectional study in The Netherlands. *Atherosclerosis* 209, 189–194 (2010).

36 Mata N, Alonso R, Badimon L *et al.* Clinical characteristics and evaluation of LDL Cholesterol treatment of the Spanish Familial Hypercholesterolemia Longitudinal Cohort Study (SAFEHEART). *Lipids Health Dis.* 10, 94 (2011).

▪▪ **Offers a clear demonstration that patients with FH are suboptimally treated in clinical practice.**

37 Leren TP, Berge KE. Subjects with molecularly defined familial hypercholesterolemia or familial defective apoB100 are not being adequately treated. *PLoS ONE* 6, e16721 (2011).

38 Stein EA, Strutt K, Southworth H *et al.* Comparison of rosuvastatin versus atorvastatin in patients with heterozygous familial hypercholesterolemia. *Am. J. Cardiol.* 92, 1287–1293 (2003).

39 Kawashiri MA, Nohara A, Noguchi T *et al.* Efficacy and safety of coadministration of rosuvastatin, ezetimibe, and colestimide in heterozygous familial hypercholesterolemia. *Am. J. Cardiol.* 109, 364–369 (2012).

40 Kastelein JJ, Akdim F, Stroes ES *et al.* Simvastatin with or without ezetimibe in familial hypercholesterolemia. *N. Engl. J. Med.* 358, 1431–1443 (2008).

41 Thompson GR; HEART-UK LDL Apheresis Working Group. Recommendations for the use of LDL apheresis. *Atherosclerosis* 198, 247–255 (2008).

42 Mabuchi H, Koizumi J, Shimizu M *et al.* Long-term efficacy of low-density lipoprotein apheresis on coronary heart disease in familial hypercholesterolemia. *Am. J. Cardiol.* 82, 1489–1495 (1998).

43 Cummings MH, Watts GF, Umpleby M *et al.* Increased hepatic secretion of very-low-density-lipoprotein apolipoprotein B-100 in heterozygous familial hypercholesterolaemia: a stable isotope study. *Atherosclerosis* 113, 79–89 (1995).

44 Sundaram M, Yao Z. Recent progress in understanding protein and lipid factors affecting hepatic VLDL assembly and secretion. *Nutr. Metab. (Lond.)* 7, 35 (2010).

45 Ito MK. ISIS 301012 gene therapy for hypercholesterolemia: sense, antisense, or nonsense? *Ann. Pharmacother.* 41, 1669–1678 (2007).

46 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 randomized, double blind, placebo-controlled trial. *Lancet* 375, 998–1006 (2010).

▪▪ **First to report the impressive results of the treatment with mipomersen of patients with homozygous FH.**

47 Akdim F, Visser ME, Tribble DL *et al.* Effect of mipomersen, an apolipoprotein B synthesis inhibitor, on low-density lipoprotein cholesterol in patients with familial hypercholesterolemia. *Am. J. Cardiol.* 105, 1413–1419 (2010).

48 Stein EA, Dufour R, Gagne C *et al.* Apolipoprotein B synthesis inhibition with mipomersen in heterozygous familial hypercholesterolemia: results of a randomized, double-blind, placebo-controlled trial to assess efficacy and safety as add-on therapy in patients with coronary artery disease. *Circulation* 126, 2283–2292 (2012).

49 Visser ME, Akdim F, Tribble DL *et al.* Effect of apolipoprotein-B synthesis inhibition on liver triglyceride content in patients with familial hypercholesterolemia. *J. Lipid Res.* 51, 1057–1062 (2010).

50 Burnett JR, Watts GF. MTP inhibition as a treatment for dyslipidaemias: time to deliver or empty promises? *Expert Opin. Ther. Targets* 11, 181–189 (2007).

51 Cuchel M, Bloedon LT, Szapary PO *et al.* Inhibition of microsomal triglyceride transfer protein in familial hypercholesterolemia. *N. Engl. J. Med.* 356, 148–156 (2007).

52 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* 381, 40–46 (2013).

▪▪ **This very recent trial extends to a longer follow-up of the evaluation of the effects of lomitapide in patients with homozygous FH.**

53 Lindholm MW, Elmén J, Fisker N *et al.* PCSK9 LNA antisense oligonucleotides induce sustained reduction of LDL cholesterol in nonhuman primates. *Mol. Ther.* 20(2), 376–381 (2012).

54 Liang H, Chaparro-Rigger J, Strop P *et al.* Proprotein convertase substillisin/kexin type 9 reduces LDL cholesterol in statin-treated hypercholesterolemic nonhuman primates. *J. Pharmacol. Exp. Ther.* 340, 228–236 (2012).

55 Stein EA, Mellis S, Yancopoulos GD *et al.* Effect of a monoclonal antibody to PCSK9 on LDL cholesterol. *N. Engl. J. Med.* 366, 1108–1118 (2012).

56 Stein EA, Gipe D, Bergeron J *et al.* Effect of a monoclonal antibody to PCSK9, REGN727/SAR236553, to reduce low-density lipoprotein cholesterol in patients with heterozygous familial hypercholesterolaemia on stable statin dose with or without ezetimibe therapy: a Phase 2 randomised controlled trial. *Lancet* 380, 29–36 (2012).

57 Raal F, Scott R, Somaratne R *et al.* Low-density lipoprotein cholesterol-lowering effects of AMG 145, a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 serine protease in patients with heterozygous familial hypercholesterolemia: the reduction of LDL C with PCSK9 inhibition in heterozygous familial hypercholesterolemia disorder (Rutherford) randomized trial. *Circulation* 126, 2408–2417 (2012).

▪▪ **Largest trial employing a PCSK9 inhibitor in FH carried out so far.**

58 Vuorio A, Kuoppala J, Kovanen PT *et al.* Statins for children with familial hypercholesterolemia. *Cochrane Database Syst. Rev.* 7, CD006401 (2010).

59 Avis HJ, Hutten BA, Gagné C *et al.* Efficacy and safety of rosuvastatin therapy for children with familial hypercholesterolemia. *J. Am. Coll Cardiol.* 55(11), 1121–1126 (2010).

60 Rodenburg J, Vissers MN, Wiegman A *et al.* Statin treatment in children with familial hypercholesterolemia; the younger, the better. *Circulation* 116, 664–668 (2007).

61 Goldberg AC, Hopkins PN, Toth PP *et al.* Familial hypercholesterolemia: screening, diagnosis and management of pediatric and adult patients. *J. Clin. Lipidol.* 5(Suppl. 3), S1–S8 (2011).

62 Daniels SR, Greer FR. Lipid screening and cardiovascular health in children. *Pediatrics* 122, 198–208 (2008).

63 Avis HJ, Vissers MN, Stein EA *et al.* A systematic review and meta-analysis of statin therapy in children with familial hypercholesterolemia. *Arterioscler. Thromb. Vasc. Biol.* 27(8), 1803–1810 (2007).

64 Watts GF, Sullivan DR, Poplawski N *et al.*; Familial Hypercholesterolaemia Australasia Network Consensus Group (Australian Atherosclerosis Society). Familial hypercholesterolaemia: a model of care for Australasia. *Atheroscler. Suppl.* 12, 221–263 (2011).

65 Descamps OS, Tenoutassa S, Stephenne X *et al.* Management of familial hypercholesterolemia in children and young adults: consensus paper developed by a panel of lipidologists, cardiologists, paediatricians, nutritionists, gastroenterologists, general practitioners and a patient organization. *Atherosclerosis* 218, 272–280 (2011).

66 McCrindle BW, Urbina EM, Dennison BA *et al.* Drug therapy of high-risk lipid abnormalities in children and adolescents: a scientific statement from the American Heart Association Atherosclerosis, Hypertension and Obesity Youth Committee, Council of Cardiovascular Disease in the Young, with the Council on Cardiovascular Nursing. *Circulation* 115, 1948–1967 (2007).

67 Raitakari OT, Juonala M, Kähönen M *et al.* Cardiovascular risk factors in childhood and carotid artery intima-media thickness in adulthood: the Cardiovascular Risk in Young Finns Study. *JAMA* 290, 2277–2283 (2003).

68 Wiegman A, de Groot E, Hutten BA *et al.* Arterial intima–media thickness in children heterozygous for familial hypercholesterolaemia. *Lancet* 363, 369–370 (2004).

69 Horton JD, Cohen JC, Hobbs HH. PCSK9: a convertase that coordinates LDL catabolism. *J. Lipid Res.* 50(Suppl.), S172–S177 (2009).

70 Vuorio A, Docherty KF, Humphries SE, Kuoppala J, Kovanen PT. Statin treatment of children with familial hypercholesterolemia. Trying to balance incomplete evidence of long-term safety and clinical accountability: are we approaching a consensus? *Atherosclerosis* 226(2), 315–320 (2012).

▪▪ **Evaluates all evidence supporting the use of statins in children with FH.**

71 Wiegman A, Hutten BA, de Groot E *et al.* Efficacy and safety of statin therapy in children with familial hypercholesterolemia: a randomized controlled trial. *JAMA* 292, 331–337 (2004).

72 Kusters DM, Homsma SJ, Hutten BA *et al.* Dilemmas in treatment of women with familial hypercholesterolaemia during pregnancy. *Neth. J. Med.* 68, 299–303 (2010).

73 Amundsen AL, Khoury J, Iversen PO *et al.* Marked changes in plasma lipids and lipoproteins during pregnancy in women with familial hypercholesterolemia. *Atherosclerosis* 189(2), 451–457 (2006).

74 Palinski W, Napoli C. The fetal origins of atherosclerosis: maternal hypercholesterolemia, and cholesterol-lowering or antioxidant treatment during pregnancy inf uence in utero programming and postnatal susceptibility to atherogenesis. *FASEB J.* 16, 1348–1360 (2002).

75 Alkemade FE, Gittenberger-de Groot AC, Schiel AE *et al.* Intrauterine exposure to maternal atherosclerotic risk factors increases the susceptibility to atherosclerosis in adult life. *Arterioscler. Thromb. Vasc. Biol.* 27, 2228–2223 (2007).

76 Thorogood M, Seed M, De Mott K. Management of fertility in women with familial hypercholesterolaemia: summary of NICE guidance. *BJOG* 116, 478–479 (2009).

77 Kusters DM, Lahsinoui HH, van de Post JA *et al.* Statin use during pregnancy: a systematic review and meta-analysis. *Expert Rev. Cardiovasc Ther.* 10, 363–378 (2012).

78 Tardif JC, McGowan M, Ceska R *et al.* Apolipoprotein B synthesis inhibition by mipomersen reduces low-density lipoprotein cholesterol when added to maximally tolerated lipid-lowering medication in patients with severe heterozygous hypercholesterolemia free. *J. Am. Coll. Cardiol.* 57(14), e492 (2011).

■ Websites

101 WHO. Familial hypercholesterolaemia (FH). Report of a second WHO consultation; Geneva; 4 September 1998. Geneva: WHO Human Genetics Programme, 1999. http://whqlibdoc.who.int/hq/1999/WHO_HGN_FH_CONS_99.2.pdf (Accessed 8 March 2013)

102 National Institute for Health and Clinical Excellence. Familial hypercholesterolaemia. Identification and management of familial hypercholesterolaemia (2009). www.nice.org.uk/CG71 (Accessed 8 March 2013)

103 UCL LDL receptor database. www.ucl.ac.uk/ldlr/LOVDv.1.1.0 (Accessed 8 March 2013)

104 National Institute of Clinical Excellence. Identification and management of familial hypercholesterolaemia e clinical guideline CG71. www.nice.org.uk/nicemedia/pdf/CG071NICEGuideline.pdf (Accessed 8 March 2013)

105 Scottish Intercollegiate Guidelines Network. Risk estimation and the prevention of cardiovascular disease. www.sign.ac.uk/pdf/sign97.pdf (Accessed 8 March 2013)