Atherosclerosis 277 (2018) 483–492

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Review article

Familial hypercholesterolemia treatments: Guidelines and new therapies

Frederick J. Raal [a], G. Kees Hovingh [b], Alberico L. Catapano [c, d, *]

[a] Carbohydrate & Lipid Metabolism Research Unit, Division of Endocrinology & Metabolism, Department of Medicine, Faculty of Health Sciences, Johannesburg Hospital, University of the Witwatersrand, Parktown, Johannesburg, South Africa
[b] Department of Vascular Medicine, Academic Medical Center, Amsterdam, the Netherlands
[c] Department of Pharmacological and Biomolecular Sciences, Università Degli Studi di Milano, Milan, Italy
[d] IRCCS Multimedica, Milan, Italy

ARTICLE INFO

Article history:
Received 18 April 2018
Received in revised form
28 May 2018
Accepted 14 June 2018

Keywords:
Familial hypercholesterolemia
Low density lipoprotein receptor
Lipid-lowering drugs
Guidelines

ABSTRACT

Familial hypercholesterolemia (FH) is a genetic disorder resulting from mutations in genes encoding proteins involved in the metabolism of low density lipoproteins (LDL) and characterized by premature cardiovascular disease due to the exposure to high levels of LDL-cholesterol (LDL-C) from birth. Thus, the early identification of FH subjects, followed by appropriate treatment is essential to prevent or at least delay the onset of cardiovascular events. However, FH is largely underdiagnosed; in addition, FH patients are frequently not adequately treated, despite the availability of several pharmacological therapies to significantly reduce LDL-C levels. Current guidelines recommend LDL-C targets for FH (either heterozygotes [HeFH] or homozygotes [HoFH]) <100 mg/dL (<2.6 mmol/L) for adults or <70 mg/dL (<1.8 mmol/L) for adults with CHD or diabetes, and <135 mg/dL (<3.5 mmol/L) for children. With the pharmacological options now available, which include statins as a first approach, ezetimibe, and the recently approved monoclonal antibodies targeting PCSK9, the guideline recommended LDL-C target levels can be achieved in the majority of heterozygous FH subjects, while for the most severe forms of homozygous FH, the addition of therapies such as lomitapide either with or without apheresis may be required.

1. Introduction

Familial hypercholesterolemia (FH) is a genetic disorder characterized by very high levels of circulating low density lipoprotein cholesterol (LDL-C) from birth. This does result in the fast development of atherosclerosis with detrimental outcomes such as myocardial infarction and death occurring early in life in patients with FH, especially in those who are not or inadequately treated [1–4]. Despite several effective cholesterol-lowering drugs now being available, a main gap in the management of this disease is the lack of early detection and appropriate pharmacological intervention of FH subjects. In fact, the most severe forms, such as homozygous FH, generally exhibit unambiguous physical signs from the childhood; in contrast, less severe forms of FH may remain hidden until the occurrence of the first cardiovascular event. Thus, the early identification of these subjects is crucial to reduce the burden of cholesterol exposure and the incidence of cardiovascular events.

Genetic defects in several genes involved in LDL metabolism may cause FH; mutations in the *LDLR* gene, encoding for the LDL receptor (LDLR) are the most common cause of FH, but mutations in the *APOB* gene and gain-of-function (GOF) mutations in the *PCSK9* gene can also result in the FH phenotype [5–7]. A rare recessive form of hypercholesterolemia (autosomal recessive hypercholesterolemia, ARH) is caused by the loss-of-function mutations in the *LDLRAP1* gene (encoding for a protein that promotes the internalization of LDLR/LDL complex) [8,9]. However, among subjects with a clinical diagnosis of FH, only 40–80%, depending on the criteria used, exhibit a mutation in one of the classical genes causative of FH, which suggests that a relatively high proportion of "mutation-negative" FH patients are likely to have a polygenic cause underlying their marked hypercholesterolemia [10,11].

The heterozygous form of FH (HeFH) has a prevalence of ~1/500

* Corresponding author. Department of Pharmacological and Biomolecular Sciences, University of Milan and IRCCS Multimedica, Via Balzaretti, 9, 20133, Milan, Italy.
E-mail address: alberico.catapano@unimi.it (A.L. Catapano).

https://doi.org/10.1016/j.atherosclerosis.2018.06.859
0021-9150/

Table 1
Summary of the guidelines in adults and children with HeFH [15].

Recommendations	Class of recommendation and level of evidence
FH is recommended to be suspected in:	I; C
patients with early CHD (<55 y men; <60 women)	
subjects with relatives with premature CVD	
subjects with relatives with xanthomas	
subjects with very high LDL-C (adults: >190 mg/dL; children >150 mg/dL)	
Diagnosis of FH is recommended to be confirmed with clinical criteria and genetic testing	I; C
Family cascade screening of an FH index case is recommended	I; C
FH patients are recommended to be treated with high-dose statin, with or without ezetimibe	I; C
LDL-C targets should be < 100 mg/dL or 70 mg/dL in presence of CVD; or alternatively, the maximal reduction with combination therapies	IIa; C
PCSK9 inhibitors should be used in FH patients at very high risk, such as those with CVD or having additional cardiovascular risk factors	IIa; C
Testing in children is recommended from age 5 y (or earlier if suspected of HoFH)	I; C
Children should be educated to a healthy lifestyle and treated with statin from 8 to 10 y; LDL-C target should be < 135 mg/dL	IIa; C

CHD: coronary heart disease; CVD: cardiovascular disease.
Class of recommendations: I: is recommended/indicated; IIa: should be considered.
Level of evidence C: consensus of opinion of the experts and/or small studies, retrospective studies, registries.

to 1/200 in the general population and is characterized by a 2–3 fold increase of LDL-C levels and the occurrence of coronary heart disease (CHD) before age 55 (60 for women) [1,2,12]; the homozygous form (HoFH) is rarer, with a prevalence of ~1/160,000–1/300,000, and HoFH patients are generally characterized by an even more severe LDL-C level phenotype. This greater cholesterol burden does result in the onset of extremely premature cardiovascular disease, with HoFH patients who suffer from a myocardial infarction well before their 10th year of age [2], particularly in HoFH patients who carry two receptor-negative mutations [2,5]. Subjects carrying mutations in *APOB* or *PCSK9* genes generally exhibit a milder phenotype [6,13].

The diagnosis of FH can be based either on clinical criteria or genetic testing; the last provides a definitive diagnosis of FH, but there are some patients with clinical diagnosis of FH in whom no mutation can be identified in the genes classically associated to this condition, suggesting the involvement of unknown genes or a polygenic cause. However, a positive genetic test allows one to discriminate a FH subject from a “normal” hypercholesterolemic individual on the one hand [14], and on the other aids in the identification of FH among relatives. Due to the high number of possible mutations causing FH and due to the possible involvement of additional genes, the phenotype of FH is highly variable, and subjects carrying the same mutation may exhibit profoundly different lipid and clinical profiles as well as different responses to the same pharmacological treatment; in addition, subjects with HoFH may present LDL-C levels well below those expected for this condition and thus may not be recognized.

2. Guidelines for the management of familial hypercholesterolemia

Based on a prevalence of 1/200-1/500, it can be estimated that there are between 14 and 34 million individuals having FH worldwide, but in most countries less than 1% are diagnosed (with some exceptions) [1]. Another major key point is that subjects with FH have an at least 10-fold increase risk of CHD, which may manifest early in life, and the risk remains high even among patients treated with statins, which suggests that they are treated with therapies that are inadequate (low dose, late in life) to achieve the LDL-C levels recommended for their category of cardiovascular risk [1].

To reduce the cumulative burden of elevated LDL-C levels and prevent or delay the onset of cardiovascular events, most guidelines recommend LDL-C targets for FH (either HeFH or HoFH) of <100 mg/dL (<2.6 mmol/L) for adults, or <70 mg/dL (<1.8 mmol/L) for adults with CHD or diabetes, and <135 mg/dL (<3.5 mmol/L) for children [1,15]. A summary of the recommendations in adults and children with FH is presented in Table 1. The most effective approach to identify new cases of FH is cascade screening of family members of a known FH subject, with a simple evaluation of LDL-C levels. Of particular importance is the early diagnosis and management of FH in children, especially in those with the homozygous form of the disease, who may present signs of cardiovascular disease very early in the life if untreated [16–19] (Table 1). A selective screening of children with family history of premature cardiovascular disease and/or high LDL-C levels is recommended; a universal screening of children for hypercholesterolemia might be also considered, for example taking advantage of visits for immunization, followed by the screening of the parents of children with total cholesterol >230 mg/dL (>6 mmol/L) [1].

In clinical practice, FH is commonly diagnosed using criteria based on familial or personal history of premature cardiovascular disease, clinical signs (tendon xanthoma, corneal arcus) and high LDL-C levels, with or without genetic testing; the pharmacological

approach is mainly driven by the LDL-C levels, and should start as early as possible [1,2]. Lifestyle interventions (low fat diet, physical activity and smoking cessation) are strongly recommended, in conjunction with cholesterol-lowering therapy, which should be started immediately at diagnosis (for children, it should be considered at 8–10 years of age) [1,2,15]. The first pharmacological approach usually involves statins (for children, only statins with safety profile for this group should be used), to which ezetimibe can be added if statin alone is insufficient to reduce LDL-C levels to the guideline recommended target. Monoclonal antibodies targeting PCSK9 have been approved for the treatment of FH as add-on to conventional lipid-lowering therapies [15]. The ESC/EAS Task Force recently updated the recommendations for the use of PCSK9 inhibitors in clinical practice and advises that a PCSK9 inhibitor may be considered in HeFH without clinically diagnosed cardiovascular disease, at high or very high CV risk, and with elevated LDL-C levels (>180 mg/dL) despite the maximal dose of statin + ezetimibe [20].

Estimates of the absolute CV risk of FH patients are based both on clinical trials and registries (such as the SAFEHEART registry in Spain), which indicate that, in subjects treated with the maximal tolerated dose of statin plus ezetimibe, the annual CV event rates are estimated at 1%, which, however, increases in the presence of additional risk factors [21]; thus, the LDL-C threshold for this decision may be lower (>140 mg/dL) if the subject has additional indices of risk severity (including diabetes, elevated Lp(a) levels, premature cardiovascular disease in first-degree relative, smoking, imaging indicators) [20]. A relevant point is to monitor the LDL-C response to the therapy, allowing possible adjustment of the drug dose [20].

For HoFH subjects, lomitapide and mipomersen can also be considered on top of maximal lipid-lowering therapy taking advantage of distinct mechanisms of action. Lipoprotein apheresis represents, when available, an adjunctive effective tool [2,15]. Finally, for the most severe cases of HoFH, liver transplantation can be considered, being a method that corrects permanently the molecular defect underlying the disease in the main organ involved in LDL clearance [2].

It is of special relevance the early identification of HoFH individuals, since the burden of very high LDL-C levels from birth may lead to the manifestation of cardiovascular disease very early in life. In fact, the cumulative LDL-C burden sufficient to cause CHD is reached in non-FH individuals later in life (55 y) compared with FH individuals, being HoFH those most exposed and may reach this LDL-C burden at age 12.5[1]. In clinically diagnosed HoFH subjects, the first cardiovascular event usually occurs during adolescence, but manifestations have been reported also in early childhood [2]. HoFH is characterized by accelerated atherosclerosis, with cholesterol and calcium deposits, fibrosis and inflammation in the aortic root and aortic valve cusps [2]; it is worth noting that the valvular and supravalvular aortic disease may continue to progress even when cholesterol levels are reduced [2]. For these reasons, the Consensus Panel of the European Atherosclerosis Society recommends that HoFH undergo regular screening for subclinical aortic and coronary heart disease [2]. Lipid-lowering therapies should be started as early as possible, considering that HoFH exhibit genetic and phenotypic heterogeneity which may translate into a high variable response to the available lipid-lowering approaches. A recent retrospective survey of lipid levels and clinical outcomes of HoFH treated with lipid-lowering therapies between 1990 and 2014 showed that the extent of reduction of cholesterol levels obtained during treatment is the major determinant of survival in these patients [22]; this observation suggests that when the approach with the combination high-dose statin plus ezetimibe fails to reduce LDL-C levels to the recommended levels, additional therapy must be added to the current lipid-lowering approach to further reduce LDL-C levels.

3. Current therapies for FH patients

3.1. Statins

Statin therapy represents the first pharmacological approach for the management of hypercholesterolemia in FH patients, and current guidelines recommend that adults are treated with the maximal tolerated dose of a high potency statin [1]. In most cases, however, statin monotherapy is insufficient to achieve the recommended LDL-C levels.

Given the mechanism of action of statins, which exert their lipid-lowering effect partly by increasing the hepatic expression of LDLR, it is expected that homozygous FH subjects carrying null mutations on *LDLR* gene would not respond. However, these patients are responsive to statins, although to a lesser extent compared with other FH patients [23–26], since statins may act via alternative mechanisms of action, such as the reduction of VLDL (and thus LDL) synthesis [25]. The LDL-C reduction observed in these patients is lower than that observed in non-FH patients (~20% *vs.* 40–60%).

Guidelines suggest that children with FH should also be treated with statins from the age of 8–10 years, starting with low doses and escalating the dose in order to reach the recommended LDL-C levels [15]. A main concern relates to the safety of statin treatment in children with FH. However a meta-analysis of 6 studies including 798 children showed that statins significantly reduced LDL-C (weighted mean difference: −30%), total cholesterol (−23%) and apoB (−25%) and no statistically significant differences were observed between statin- and placebo-treated children regarding adverse events, sexual development, muscle toxicity or liver toxicity [27]. The efficacy of rosuvastatin, which was not included in the described meta-analysis, has been evaluated in HeFH children and adolescents, resulting in a 35–45% reduction of LDL-C levels, a significantly lower progression of carotid intima-media thickening and no adverse effects on growth or sexual maturation after 2 years of treatment [28,29]. Rosuvastatin reduced LDL-C levels also in children and adolescents with HoFH (mean reduction 22.3%); those having a residual LDLR activity had the highest reduction (23.5%), but those carrying two LDLR null mutations also responded (14% reduction) [30]. Similarly, pitavastatin dose-dependently reduced LDL-C levels in children aged 6–17 years, with a safety profile similar to the placebo group [31,32]. It is worth noting that, in a retrospective study conducted in patients with HeFH, the use of a moderate-to high-intensity statin therapy reduced the risk of coronary artery disease and mortality by 44% [33]; however, prospective trials on cardiovascular outcomes in FH treated with statins are still lacking.

Despite statins reduce LDL-C levels in FH subjects, a small proportion of FH patients achieve the recommended LDL-C level targets with statin monotherapy, and thus they remain with a high residual cardiovascular risk, as recently reported in a cohort of consecutive HeFH patients treated with maximal tolerated lipid-lowering therapy, mainly statins, with a median years of statin use and follow-up of 9.5 years [34]. These patients exhibited LDL-C levels well above those recommended by current guidelines, and, additionally, have increased levels of Lp(a) which are not affected by statins and may contribute to the residual risk observed [35,36]. These observations suggest the need of a pharmacological approach which combines drugs able to reduce LDL-C levels by different mechanisms of action [1,37].

3.2. Ezetimibe

Ezetimibe inhibits the intestinal uptake of dietary and biliary cholesterol by inhibiting the Niemann-Pick C1 like 1 (NPC1L1)

transporter, which leads to a reduced delivery of cholesterol to the liver, which in turn upregulates LDLR expression and results in the reduction of LDL-C levels. The landmark trial on ezetimibe was the IMPROVE-IT, which compared the effect of ezetimibe added to simvastatin to simvastatin alone in patients with a recent acute coronary syndrome and reported a significant reduction of LDL-C levels and cardiovascular event rate in patients treated with the combination therapy [38]. To date, it is unclear whether the combination statin/ezetimibe may have an impact also on intima-media thickness progression [39–41], but the PRECISE-IVUS trial, performed in patients with coronary artery disease and assessing the effect of ezetimibe in combination with atorvastatin *versus* atorvastatin monotherapy, reported a greater coronary plaque regression in subjects treated with the combination therapy [42]. These data support the recommendation of giving ezetimibe in combination with a statin in FH patients, resulting in an additional reduction (10–15%) of LDL-C levels [39,43,44], and indicate ezetimibe as the first non-statin lipid lowering drug, without any safety concerns. It is worth noting that the combination ezetimibe + statin is effective also in adolescents with HeFH, who showed a greater LDL-C level reduction compared with the treatment with simvastatin alone (at week 33: −54.0% vs −38.1%, $p < 0.01$) [45]. Both treatments were well tolerated and there were no clinically relevant signs of growth, sexual maturation or steroid hormones perturbation [45].

3.3. PCSK9 inhibitors

PCSK9 is a protein mainly expressed in the liver and plays a relevant role in the expression of LDLR; in fact, it binds LDLR expressed on the surface of hepatocytes and targets it for degradation. As a consequence, high levels of PCSK9 are associated with hypercholesterolemia, and gain-of-function (GOF) mutations in the *PCSK9* gene are a cause of familial hypercholesterolemia [46] and increased cardiovascular risk [47]. On the contrary, loss-of-function (LOF) mutations are associated with reduced LDL-C plasma levels and lower risk of coronary heart disease [48,49], indicating PCSK9 as a possible pharmacological target for the treatment of hypercholesterolemia. Several PCSK9 inhibitors have been developed; such inhibitors are either monoclonal antibodies (evolocumab and alirocumab) which, by binding to circulating PCSK9, prevent its interaction with surface LDLR, or a siRNA molecule (inclisiran) which inhibits the intracellular synthesis of PCSK9. Monoclonal antibodies have been tested in a high variety of hypercholesterolemic populations, including subjects with FH (Table 2).

The evolocumab clinical trial program named PROFICIO (Program to Reduce LDL-C and Cardiovascular Outcomes Following Inhibition of PCSK9 in different Populations) included phase 3 trials to evaluate evolocumab in subjects with FH [50]. The RUTHERFORD-2 (Reduction of LDL-C With PCSK9 Inhibition in Heterozygous Familial Hypercholesterolemia Disorder Study-2, NCT01763918) trial was performed in HeFH patients on stable lipid lowering therapy and a fasting LDL-C ≥100 mg/dL (≥2.6 mmol/L) randomized to evolocumab or placebo. At week 12, LDL-C levels were reduced by ~60% compared with placebo and were independent of the underlying type of mutation (LDLR negative or defective) [51]. The TESLA (Trial Evaluating PCSK9 antibody in Subjects With LDL Receptor Abnormalities, NCT01588496) part A study, performed in HoFH patients, showed reductions of 16.5% and 13.9% with evolocumab 420 mg Q4W and Q2W, respectively [52]. However, while subjects carrying defective LDLR mutations had a significant decrease of LDL-C (−22.9% and −23.6%), apoB (−18.3% and −17.9%) and Lp(a) (−10.0% and −18.7%) in both dosing regimens, the two patients carrying negative LDLR mutations exhibited only reductions in Lp(a) levels, but not apoB or LDL-C [52]. It should be acknowledged, however, that the responses in these two patients differed, which suggests that other factors are determinants of the grade of response [52]. This finding was confirmed in the TESLA part B study [53], in which HoFH patients treated with evolocumab for 12 weeks had LDL-C levels reduced by 30.9% [53]; when analyzed according to the LDLR function, patients with a receptor defective mutation in one or both alleles were the most responsive to the therapy with evolocumab, while those carrying at least one receptor negative mutation had a lower reduction (−40.8% vs −24.5%), and the only patient carrying LDLR-negative mutations in both alleles, as well as the patient with autosomal recessive hypercholesterolemia did not respond to the therapy [53]. Even more interestingly, patients carrying the same mutations in homozygosity exhibited a heterogeneous response to the therapy (−7.1% up to −56%), which, again, shows that the response to the medication is not uniform and that additional factors are explaining the observed effect [53]. This finding has been recently addressed in an analysis of 22 HoFH patients from the ongoing TAUSSIG study (Trial Assessing Long Term Use of PCSK9 Inhibition in Subjects with Genetic LDL Disorders, NCT01624142) [54]. Lymphocytes isolated from subjects carrying the same mutations exhibit a variable expression of LDLR on their surface, which in turn negatively correlated with the levels of circulating LDL-C both pre- and post-treatment, suggesting that residual LDLR amount and function are the main determinants of LDL clearance in HoFH [54]. No anti-antibodies were observed in these subjects, thus it can be excluded a reduction of evolocumab activity due to neutralization, but rather indicates that other modifications in genes involved in LDL metabolism may play a role [54]. Another interesting observation is the lack of correlation between LDL-C and Lp(a) levels, which suggests that the residual

Table 2
Effects of PCSK9 inhibitors evolocumab and alirocumab in FH.

Clinical trial	Subjects	LDL-C (% treatment difference)	Lp(a) (% treatment difference)
EVOLOCUMAB			
RUTHERFORD-2 [51]	HeFH (12 weeks)	140 mg Q2W: −59.2% (p<0.0001) 420 mg Q4W: −61.3% (p<0.0001)	140 mg Q2W: −31.6% (p<0.0001) 420 mg Q4W: −28.2% (p<0.0001)
TESLA part A [52]	HoFH (36 weeks)	Q4W: −16.5%* Q2W: −13.9%*	Q4W: −11.7%* Q2W: −18.6%*
TESLA part B [53]	HoFH (12 weeks)	−30.9% (p<0.0001)	−11.8% (p=0.09)
TAUSSIG	Severe FH (5 years)	ONGOING	
ALIROCUMAB			
ODYSSEY FH I and FH II [57]	HeFH (78 weeks)	FH I: −57.9% (p<0.0001) FH II: −51.4% (p<0.0001)	FH I: 17.7% (p<0.0001) FH II: −20.3% (p<0.0001)
ODYSSEY HIGH FH [58]	HeFH (78 weeks)	−39.1% at week 24 (p<0.0001)	−14.8% (p=0.0164)
ODYSSEY LONG TERM [60]	HeFH (78 weeks)	−61.9% at week 24 (p<0.001)	−25.6% (p<0.001)
ODYSSEY OLE	HeFH (176 weeks)	ONGOING	

Q2W: every 2 weeks; Q4W: every 4 weeks; *: % change from baseline.

LDLR activity is not a significant determinant for Lp(a) clearance in HoFH, as observed in a previous study [52,54].

The TAUSSIG study is an open-label study evaluating the long-term (5 years) efficacy and safety of evolocumab in HoFH patients with LDL-C levels not controlled by current lipid-lowering therapy (statin alone or in combination with ezetimibe). An interim analysis showed that evolocumab produced a stable long-term reduction of LDL-C levels [55]; after a 1.7 years mean exposure to evolocumab, a 2.14%/year cardiovascular event rate was observed, which is lower than expected based on the anticipated risk in these patients. This may reflect the benefit of aggressive lipid-lowering effects with high-dose statin, ezetimibe, and PCSK9-inhibitor therapy in these patients at very high risk for cardiovascular disease [56].

Similarly to evolocumab, the ODYSSEY clinical trial program for alirocumab included some studies conducted specifically in FH patients. In the ODYSSEY FH I and FH II (Study of Alirocumab (REGN727/SAR236553) in Patients With HeFH Who Are Not Adequately Controlled With Their Lipid-Modifying Therapy, NCT01623115 and NCT01709500) randomized, double-blind studies where HeFH patients with inadequate LDL-C control despite maximally tolerated lipid-lowering therapy were enrolled, the effect of alirocumab was evaluated at 78 weeks [57]. LDL-C levels were significantly reduced at week 24 (FH I: −57.9% *vs.* placebo, FH II: −51.4% vs placebo), and these reductions were maintained up to week 78; a high percentage of patients achieved LDL-C <70 mg/dL (<1.8 mmol/L) (59.8% in FH I and 68.2% in FH II, *vs.* 0.8% and 1.2%, respectively, with placebo) [57]. Alirocumab also reduced apoB, non-HDL-C and Lp(a) [57]. The ODYSSEY HIGH FH (Efficacy and Safety of Alirocumab (SAR236553/REGN727) Versus Placebo on Top of Lipid-Modifying Therapy in Patients With Heterozygous Familial Hypercholesterolemia, NCT01617655) enrolled HeFH patients with LDL-C ≥160 mg/dL who received alirocumab or placebo for 78 weeks; a 39.1% reduction was observed at week 24 and maintained up to week 78, with a good tolerance and adverse events comparable between groups [58]. In the alirocumab group, 41% of patients reached LDL-C <70 mg/dL (for very high risk) or <100 mg/dL (for high risk patients) [58]. HeFH patients undergoing regular lipoprotein apheresis showed reduction of their LDL-C levels when treated with alirocumab, leading to apheresis discontinuation (63.4% of patients) or reduction (92.7%) [59]. Among the high CV risk patients enrolled in the ODYSSEY LONG TERM study (Safety and Tolerability of Alirocumab (SAR236553/REGN727) Versus Placebo on Top of Lipid-Modifying Therapy in High Cardiovascular Risk Patients With Hypercholesterolemia, NCT01507831), HeFH and non-HeFH patients treated with alirocumab showed similar LDL-C level reductions (mean difference *vs.* placebo: 63.2% and 61.5%, respectively); in a *post hoc* analysis there was evidence of reduced cardiovascular events with alirocumab in the whole study population (1.7% *vs.* 3.3%, HR 0.52, nominal p=0.02)[60]. The ongoing ODYSSEY OLE (Open Label Study of Long Term Safety Evaluation of Alirocumab, NCT01954394) is evaluating the long-term safety of alirocumab up to 176 weeks in HeFH patients. Two recent analyses of the effect of alirocumab based on the type of mutation causing HeFH showed that the response to alirocumab was independent of the mutation status [61], and that in subjects thought to have HeFH but found to have two mutations in either the LDLR (homozygous or compound heterozygous LDLR mutations provided at least one mutation was defective) or mutations in LDLR plus a mutation in either apoB or PCSK9 (double heterozygous FH), and thus having a residual LDLR function, alirocumab treatment provides substantial reductions in LDL-C levels [62].

Altogether, these data suggest that FH patients, in particular HeFH, may benefit most from additional LDL-C-lowering by means of anti-PCSK9 inhibitor therapy, as it may induce an additional ~60% LDL-C reduction in HeFH patients who are already treated with the maximal tolerated lipid-lowering therapy. This translates into over 80% of these patients being able to achieve recommended LDL-C targets [51,57]. Although it is still unclear whether reducing Lp(a) levels may translate into a cardiovascular benefit, the treatment with antibodies targeting PCSK9 is also effective in reducing this atherogenic lipoprotein whose levels are commonly increased in these high risk patients [63].

3.4. Mipomersen

Mipomersen is a second-generation antisense oligonucleotide which binds the coding region of human apoB mRNA and triggers its degradation, which results in the reduction of all atherogenic apoB-containing lipoproteins (LDL, but also VLDL and Lp (a)). The reduction of LDL-C levels mediated by mipomersen is independent of LDLR expression [64]. Mipomersen is not metabolized by the cytochrome system and is not considered an inhibitor of major CYP isoenzymes, thus no clinically relevant interactions between mipomersen and statins or ezetimibe are expected [65].

Due to its mechanism of action being independent of LDLR expression, it has been developed as adjunct treatment for patients with FH, particularly for those with HoFH (Table 3). A phase 3 study showed that mipomersen was effective in HoFH on low-fat diet and maximal tolerated cholesterol-lowering therapy; LDL-C levels decreased by 21.3% (p=0.0003) and Lp(a) by 23.2% (p=0.0013) compared with placebo [66]; non-HDL and VLDL were also significantly reduced [66]. Mipomersen provided sustained reductions of LDL-C, Lp(a) and other lipids for up to 104 weeks [67].

The most commonly observed adverse events following mipomersen treatment are injection-site reactions [66,68]. Some patients experienced elevations in alanine aminotransferase, but such increases did not associate with clinically significant changes in other parameters of liver function and were largely reversible [66,69–71]. In addition, some patients enrolled in the short-term studies showed a modest increased content (6–12%) of hepatic fat [69,72]; liver biopsies performed in patients with severe hypercholesterolemia during mipomersen treatment revealed a simple steatosis, without signs of inflammation or fibrosis [73]. Both transaminase increase and hepatic steatosis did not progress during long-term treatment and returned to baseline after mipomersen discontinuation [67,74,75]. A *post hoc* analysis of prospectively collected data of subjects enrolled in an open label extension study showed that mipomersen significantly reduced major adverse cardiac event rate (−85%) [76].

3.5. Lomitapide

The microsomal triglyceride transfer protein (MTP) is a lipid transfer protein localized in the endoplasmic reticulum of hepatocytes and enterocytes, playing a key role in the assembly and secretion of apolipoprotein-B-containing lipoproteins in both the liver (VLDL) and intestine (chylomicrons) [77]. Individuals carrying loss-of-function mutations in the gene encoding for MTP (*MTTP*) are characterized by hypocholesterolemia and reduced levels of circulating apoB-containing lipoproteins [78], suggesting MTP as a pharmacological target for the treatment of hypercholesterolemia. This led to the development of lomitapide, an MTP inhibitor that has been approved for the treatment of HoFH [79] (Table 3).

Lomitapide reduces LDL-C levels by an LDLR-independent mechanism. Due to its mechanism of action, lomitapide treatment results in the impairment of TG secretion from the liver, leading to the accumulation of hepatic TG, steatosis and increased in hepatic enzymes [80,81]. Lomitapide is a weak inhibitor of cytochrome P450 3A4 and is metabolized primarily by this enzyme

Table 3
Effects of mipomersen and lomitapide in FH subjects.

Subjects	Duration	LDL-C (% change from baseline)	Lp(a) (% change from baseline)
HoFH [66]	Mipomersen 26 weeks	−24.7% (p=0.0003)	−31.1% (p=0.0013)
HeFH + HoFH [67]	Mipomersen 104 weeks	−28% (p<0.001)	−14% (p<0.001)
HoFH [84]	Lomitapide 26 + 52 weeks	−50% at week 26 (p<0.0001) −38% at week 78 (p=0.0001)	−15% at week 26 (p=0.0003) −0.5% at week 78 (n.s.)
HoFH (NCT02399852)	Lomitapide 5 years	ONGOING	

CAD: coronary artery disease; HC: hypercholesterolemia; n.s.: not significant.

[82,83], emphasizing the need for careful monitoring of possible adverse effects during coadministration of lomitapide and statins.

The first phase 3 pivotal study of lomitapide in HoFH, that included a 26-week efficacy study and a 52-week safety study, showed a robust and durable reduction of LDL-C levels (50% at week 26 and 38% at week 78) as well as other lipids (including total cholesterol, VLDL-C, non-HDL-C, TG and apoB) [84]; some patients were able to suspend or delay apheresis treatment [84]. The main adverse events included gastrointestinal events (diarrhoea), elevations of hepatic enzymes and an increase in mean hepatic fat, measured by nuclear magnetic resonance spectroscopy [84]. The long term clinical relevance of this steatosis remains to be examined, as it may cause fibrosis and cirrhosis in the long run. An extension trial, aimed at evaluating the relevance of hepatic fat accumulation, reported a sustained LDL-C level reduction up to 168 weeks accompanied by an increased median hepatic fat content which, however, was not correlated with changes in hepatic enzymes or overt liver disease [85]. To further establish the efficacy and safety of long-term lomitapide treatment, an observational exposure registry (LOWER: Lomitapide Observational Worldwide Evaluation Registry) will follow lomitapide-treated HoFH patients for at least 10 years [86].

The unclear clinical consequences of both mipomersen and lomitapide side effects on liver led to the requirement for post-marketing observation studies, a black-box warning, and a Risk Evaluation and Mitigation Strategy (REMS) [87].

3.6. LDL apheresis

Lipoprotein apheresis is the physical removal of lipoproteins from the blood and represents an important tool for the treatment of FH patients in which the pharmacological approach is not sufficient to reduce significantly LDL-C levels; it is indicated particularly for HoFH patients or severe HeFH who do not respond to statins or are statin-intolerant. Following apheresis, both LDL-C and Lp(a) levels significantly decrease by 50–70%, but return to baseline levels during the period to the next apheresis procedure [88]. The combination of lipoprotein apheresis with lipid-lowering drugs may thus further improve the lipid profile and reduce the cardiovascular risk; the most common adverse effects are mild-to-severe hypotension and nausea [88]; however, being an invasive procedure, it can negatively impact the quality of life. Clinical trials with PCSK9 inhibitors have suggested that, due to their high lipid-lowering effect, they can allow to reduce the frequency or even delay apheresis treatments [59].

3.7. Liver transplantation

Since over 90% of the total LDLR is localized in hepatic cells, liver transplantation is the only treatment to normalize the LDL-C levels, as it leads to the almost complete replacement of dysfunctional LDLR [89,90], however little is known about the long-term effect of this procedure for this specific indication. After liver transplantation, LDL-C levels reduce dramatically [89,91]; however, this procedure must be adopted before the onset of cardiovascular complications. In fact, despite lipid normalization, cardiovascular events may occur in the presence of established atherosclerosis before the liver transplantation, and the vascular stenosis may progress [92]. One case study showed a patient who was compound heterozygous for a large deletion and a mutation resulting in a 10% residual LDLR activity who presented with severe heart failure with advanced atherosclerotic disease and underwent a combined heart and liver transplantation [93]. LDL-C levels dramatically reduced 10 days post-transplantation (from 13 mmol/L [503 mg/dL] to 2.1 mmol/L [81 mg/dL])[93]; after 20 years, LDL-C levels were 4.3 mmol/L (166 mg/dL), and no signs of cardiovascular disease were present [93].

Due to the significant clinical challenges of organ transplantation (due to the need of life-long immunosuppressive therapy), it remains an accepted option only for the treatment of HoFH patients unresponsive to conventional lipid-lowering therapy and possibly before the onset of significant cardiovascular disease.

3.8. Novel emerging therapies for the treatment of FH

Inclisiran (ALN-PCSsc) is a long-acting synthetic small interfering RNA designed to bind specific receptors in the liver and which acts by inhibiting the synthesis of PCSK9 [94]; in patients at high cardiovascular risk with high LDL-C levels, inclisiran was highly effective in reducing LDL-C levels [95], and rates of adverse events were comparable between inclisiran and placebo groups [95]. Inclisiran is currently under evaluation in the phase 3 study ORION-9 (NCT03397121) in patients with HeFH and elevated LDL-C to assess the efficacy, safety, and tolerability of subcutaneous (SC) injection(s) of inclisiran, and in the phase 2 ORION-2 (NCT02963311) in HoFH.

Angiopoietin-like 3 (ANGPTL3) is a hepatic protein playing a key role in lipoprotein metabolism through the inhibition of both lipoprotein lipase (LPL) and endothelial lipase (EL) activity, and loss-of-function (LOF) variants of *ANGPTL3* gene are associated with reduced plasma levels of TG and LDL-C. Heterozygous carriers of ANGPTL3 LOF mutations have a 34% reduction in odds of CAD, and subjects in the lowest tertile of ANGPTL3 levels have reduced odds of myocardial infarction compared with subjects in the highest tertile [96], indicating ANGPTL3 as a possible pharmacological target for the treatment of hypercholesterolemia. Interestingly, ANGPTL3 modulates LDL-C levels independently of the LDLR [97], which suggests that pharmacological inhibition of ANGPTL3 might be effective in reducing LDL-C levels in patients with HoFH. Thus, a 4-week treatment of nine HoFH patients already receiving aggressive lipid-lowering therapies (including statins, ezetimibe, lomitapide and PCSK9 mAbs) with evinacumab, a monoclonal antibody to ANGPTL3, was shown to reduce significantly LDL-C levels (overall mean reduction: 49% ± 23)[98]. Evinacumab was highly effective also in 2 null homozygotes and 1 compound heterozygotes carrying 2 null mutations [98]. It is worth noting that the treatment with evinacumab resulted in a significant reduction of PCSK9 levels, suggesting that part of the observed effect on LDL-C

levels may be ascribed to changes in PCSK9[98].

Bempedoic acid is an ATP citrate lyase (ACL) inhibitor that reduces cholesterol biosynthesis and lowers LDL-C by up-regulating the LDLR. Phase 2 studies have reported LDL-C reduction by up to 30% in monotherapy, almost 50% in combination with ezetimibe and an additional 20% on top of statins. The ongoing Phase 3 program for bempedoic acid consists of four studies including almost 3600 patients at high cardiovascular risk having hypercholesterolemia despite maximal tolerated lipid-lowering therapy and atherosclerotic cardiovascular disease (ASCVD) and/or HeFH, or who are high risk primary prevention. The 12-week study reported a 28% reduction of LDL-C levels compared with placebo [99]; Interestingly, bempedoic acid also significantly decreases the levels of the inflammatory marker high sensitivity C-reactive protein (hs-CRP) by 33% compared with placebo [99]. Results from the other studies are expected this year.

Despite significant therapeutic advancement over the last few years, HoFH remains a difficult to treat condition for many of these patients, particularly for those carrying null LDLR mutations or with very low residual LDLR activity, as they cannot respond adequately to conventional lipid-lowering therapies based on the upregulation of LDLR. Thus, HoFH is an ideal candidate for liver-directed gene therapy, which has the potential to deliver functional copies of the human *LDLR* gene to the liver, where about 75% of the whole body LDL receptors are expressed [100]. This treatment ideally requires a single administration that may have a long-lasting effect on LDL-C levels. An ongoing study is evaluating a 52-week safety of this gene therapy investigational product and assessing preliminary evidence of LDL-C lowering, with a total follow-up of 5 years. Based on the results obtained with several AAV gene therapy agents, a complete reversal of the disease phenotype is not expected; however, a clinically significant LDL-C reduction and increase in the response to current lipid-lowering therapies are anticipated.

Gemcabene is a lipid-regulating molecule that enhances the clearance of VLDL by reducing hepatic apolipoprotein C-III (apoC-III) messenger RNA (mRNA), resulting in lower LDL-C levels [101]. Despite it was evaluated in clinical trials in the early 2000s, the results of these studies were not published. However, in 2016 a phase 2 trial was announced to investigate the efficacy, safety, and tolerability of gemcabene in HoFH patients on stable lipid-lowering therapies (statins and/or ezetimibe and/or PCSK9i) (COBALT-1). After 12-weeks, gemcabene (300, 600, and 900 mg) reduced significantly LDL-C levels (25–30%), with mild-to-moderate adverse events [102]. A 10–15% reduction was observed in three patients with null (<2%) receptor activity [102]. The ROYAL-1 study evaluated the effect of gemcabene 600 mg in patients with HeFH, ASCVD with hypercholesterolemia not adequately controlled on high-intensity or moderate-intensity stable statin therapy [103]. Mean percent change in LDL-C levels with gemcabene was −17.2% (vs −5.5% with placebo); a high decrease in hs-CRP was also observed (−40% vs −6.1% for placebo) [103], with a good safety profile and without signs of drug-drug interaction with statin.

3.9. Cardiovascular risk stratification in FH patients

CHD is the main cause of mortality and morbidity in FH individuals; compared with the general population, those with a clinical diagnosis of definite FH have a significantly higher coronary mortality, with a mean age of onset of CHD of 55 years in men and 65 years in women [1]. It has been shown that in FH primary prevention is more effective than secondary prevention started after the occurrence of a cardiovascular event (48% reduction in CHD mortality vs 25%) [104], and that starting a pharmacological approach early in life is more effective in preventing any excess coronary mortality in early adulthood [105].

The extent of atherosclerosis and CHD risk appears to be higher in patients with monogenic FH compared with subjects with polygenic hypercholesterolemia [14]; in addition, for any given LDL-C level, the risk for CAD is significantly higher in carriers of an FH mutation *versus* non-carriers, which may be explained by a prolonged exposure to high LDL-C levels [14]; thus, improving the identification of the possible genetic cause of FH and establishing the CHD risk in monogenic FH and polygenic hypercholesterolaemia may help to identify the subjects at highest risk for a better pharmacological approach.

Classical cardiovascular risk factors, such as age, gender, smoking, and hypertension play a role in determining the global CV risk in FH patients, beyond their LDL-C levels [106,107]. Thus, among subjects carrying the same mutation, the severity and clinical manifestation of the pathology may vary consistently. Lp(a) levels, which are an independent cv risk factor, are increased in FH patients, particularly in those who manifest an early CHD event [36,108], and thus its measurement is recommended in these patients for a better risk stratification [109]. In addition, FH patients have an increased carotid intima-media thickness [19,110], a biomarker of subclinical atherosclerosis, and its evaluation by non-invasive imaging methods may help to identify subjects with advanced atherosclerosis and, thus, at increased CV risk.

Invasive methods, which are not recommended for asymptomatic patients, can be used, by contrast, for those patients presenting with clinical signs of cardiac event. There is limited evidence available in using other cardiac biomarkers, such as high-sensitivity C reactive protein and inflammatory cytokines in risk stratification of asymptomatic patients with FH, or calcium score which have been examined only in few small studies.

4. Conclusions

Current guidelines strongly support treatment of FH with goals of 100 (2.56 mmol/L) and 70 mg/dL (1.86 mmol/L) according to the risk levels. Up to 3 decades ago, the treatment of severe hypercholesterolemia in FH was a clinical dilemma. The availability of statins and later on of other pharmacological interventions has produced a dramatic shift in our capability of controlling LDL levels even in homozygous patients, with a few exceptions in which apheresis is still required. The most important challenge, however, remains diagnosis, which is not optimally performed worldwide. As a consequence, subjects with FH remain undiagnosed and therapy is not fully implemented.

Conflicts of interest

F.J.R. has received research grants from Amgen, Sanofi, Regeneron Pharmaceuticals, Inc. and the Medicines Company, has served on and received honoraria for a Speakers Bureau and consultant/advisory boards for Amgen, Sanofi, Regeneron Pharmaceuticals, Inc., and the Medicines Company.

G.K.H. reports consulting and/or lecture fees from Amgen Inc, Regeneron/Sanofi, and Pfizer related to PCSK9 inhibitors, and institutional research funding related to PCSK9 inhibitor clinical trials from Amgen Inc, Sanofi, Eli Lilly, and Pfizer.

A.L.C. has received honoraria, lecture fees, or research grants from: Abbot, Aegerion, Amgen, AstraZeneca, Bayer, Eli Lilly, Genzyme, Ionis, Kowa, Mediolanum, Meda, Menarini, Merck, Pfizer, Recordati, Regeneron, Sanofi, SigmaTau.

Financial support

The work of ALC is supported by: Fondazione Cariplo 2015-0524

and 2015-0564; H2020 REPROGRAM PHC-03-2015/667837-2; ERA-NET ER-2017-2364981.

References

[1] B.G. Nordestgaard, M.J. Chapman, S.E. Humphries, 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. 34 (2013), 3478–3490a.

[2] M. Cuchel, E. Bruckert, H.N. Ginsberg, et al., Homozygous familial hypercholesterolaemia: new insights and guidance for clinicians to improve detection and clinical management. A position paper from the Consensus Panel on Familial Hypercholesterolaemia of the European Atherosclerosis Society, Eur. Heart J. 35 (2014) 2146–2157.

[3] A. Wiegman, S.S. Gidding, G.F. Watts, et al., Familial hypercholesterolaemia in children and adolescents: gaining decades of life by optimizing detection and treatment, Eur. Heart J. 36 (2015) 2425–2437.

[4] H.W. Krogh, L. Mundal, K.B. Holven, et al., Patients with familial hypercholesterolaemia are characterized by presence of cardiovascular disease at the time of death, Eur. Heart J. 37 (2016) 1398–1405.

[5] A.D. Sniderman, S. Tsimikas, S. Fazio, The severe hypercholesterolemia phenotype: clinical diagnosis, management, and emerging therapies, J. Am. Coll. Cardiol. 63 (2014) 1935–1947.

[6] A.J. Whitfield, P.H. Barrett, F.M. van Bockxmeer, et al., Lipid disorders and mutations in the APOB gene, Clin. Chem. 50 (2004) 1725–1732.

[7] L.H. Andersen, A.R. Miserez, Z. Ahmad, et al., Familial defective apolipoprotein B-100: a review, J. Clin. Lipidol. 10 (2016) 1297–1302.

[8] C.K. Garcia, K. Wilund, M. Arca, et al., Autosomal recessive hypercholesterolemia caused by mutations in a putative LDL receptor adaptor protein, Science 292 (2001) 1394–1398.

[9] R. Fellin, M. Arca, G. Zuliani, et al., The history of Autosomal Recessive Hypercholesterolemia (ARH). From clinical observations to gene identification, Gene 555 (2015) 23–32.

[10] P.J. Talmud, S. Shah, R. Whittall, et al., Use of low-density lipoprotein cholesterol gene score to distinguish patients with polygenic and monogenic familial hypercholesterolaemia: a case-control study, Lancet 381 (2013) 1293–1301.

[11] M. Futema, S. Shah, J.A. Cooper, et al., Refinement of variant selection for the LDL cholesterol genetic risk score in the diagnosis of the polygenic form of clinical familial hypercholesterolemia and replication in samples from 6 countries, Clin. Chem. 61 (2015) 231–238.

[12] S. Singh, V. Bittner, Familial hypercholesterolemia-epidemiology, diagnosis, and screening, Curr. Atherosclerosis Rep. 17 (2015) 482.

[13] H. Mabuchi, A. Nohara, T. Noguchi, et al., Genotypic and phenotypic features in homozygous familial hypercholesterolemia caused by proprotein convertase subtilisin/kexin type 9 (PCSK9) gain-of-function mutation, Atherosclerosis 236 (2014) 54–61.

[14] A.V. Khera, H.H. Won, G.M. Peloso, et al., Diagnostic yield and clinical utility of sequencing familial hypercholesterolemia genes in patients with severe hypercholesterolemia, J. Am. Coll. Cardiol. 67 (2016) 2578–2589.

[15] A.L. Catapano, I. Graham, G. De Backer, et al., 2016 ESC/EAS guidelines for the management of dyslipidaemias: the Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) developed with the special contribution of the European Assocciation for Cardiovascular Prevention & Rehabilitation (EACPR), Atherosclerosis 253 (2016) 281–344.

[16] A. Wiegman, E. de Groot, B.A. Hutten, et al., Arterial intima-media thickness in children heterozygous for familial hypercholesterolaemia, Lancet 363 (2004) 369–370.

[17] S. de Jongh, M.R. Lilien, J. op't Roodt, et al., Early statin therapy restores endothelial function in children with familial hypercholesterolemia, J. Am. Coll. Cardiol. 40 (2002) 2117–2121.

[18] I. Narverud, K. Retterstol, P.O. Iversen, et al., Markers of atherosclerotic development in children with familial hypercholesterolemia: a literature review, Atherosclerosis 235 (2014) 299–309.

[19] D.M. Kusters, A. Wiegman, J.J. Kastelein, et al., Carotid intima-media thickness in children with familial hypercholesterolemia, Circ. Res. 114 (2014) 307–310.

[20] U. Landmesser, M.J. Chapman, J.K. Stock, et al., 2017 Update of ESC/EAS Task Force on practical clinical guidance for proprotein convertase subtilisin/kexin type 9 inhibition in patients with atherosclerotic cardiovascular disease or in familial hypercholesterolaemia, Eur. Heart J. 39 (2018) 1131–1143.

[21] L. Perez de Isla, R. Alonso, N. Mata, et al., Predicting cardiovascular events in familial hypercholesterolemia: the SAFEHEART registry (Spanish familial hypercholesterolemia cohort study), Circulation 135 (2017) 2133–2144.

[22] G.R. Thompson, D.J. Blom, A.D. Marais, et al., Survival in homozygous familial hypercholesterolaemia is determined by the on-treatment level of serum cholesterol, Eur. Heart J. 39 (2018) 1162–1168.

[23] M.D. Feher, J.C. Webb, D.D. Patel, et al., Cholesterol-lowering drug therapy in a patient with receptor-negative homozygous familial hypercholesterolaemia, Atherosclerosis 103 (1993) 171–180.

[24] F.J. Raal, G.J. Pilcher, D.R. Illingworth, et al., Expanded-dose simvastatin is effective in homozygous familial hypercholesterolaemia, Atherosclerosis 135 (1997) 249–256.

[25] F.J. Raal, A.S. Pappu, D.R. Illingworth, et al., Inhibition of cholesterol synthesis by atorvastatin in homozygous familial hypercholesterolaemia, Atherosclerosis 150 (2000) 421–428.

[26] A.D. Marais, F.J. Raal, E.A. Stein, et al., A dose-titration and comparative study of rosuvastatin and atorvastatin in patients with homozygous familial hypercholesterolaemia, Atherosclerosis 197 (2008) 400–406.

[27] H.J. Avis, M.N. Vissers, E.A. Stein, et al., A systematic review and meta-analysis of statin therapy in children with familial hypercholesterolemia, Arterioscler. Thromb. Vasc. Biol. 27 (2007) 1803–1810.

[28] M.J. Braamskamp, G. Langslet, B.W. McCrindle, et al., Efficacy and safety of rosuvastatin therapy in children and adolescents with familial hypercholesterolemia: results from the CHARON study, J. Clin. Lipidol. 9 (2015) 741–750.

[29] M. Braamskamp, G. Langslet, B.W. McCrindle, et al., Effect of rosuvastatin on carotid intima-media thickness in children with heterozygous familial hypercholesterolemia: the CHARON study (hypercholesterolemia in children and adolescents taking rosuvastatin open label), Circulation 136 (2017) 359–366.

[30] E.A. Stein, E.J. Dann, A. Wiegman, et al., Efficacy of rosuvastatin in children with homozygous familial hypercholesterolemia and association with underlying genetic mutations, J. Am. Coll. Cardiol. 70 (2017) 1162–1170.

[31] M.J. Braamskamp, C. Stefanutti, G. Langslet, et al., Efficacy and safety of pitavastatin in children and adolescents at high future cardiovascular risk, J. Pediatr. 167 (2015) 338–343 e335.

[32] M. Harada-Shiba, J.J.P. Kastelein, G.K. Hovingh, et al., Efficacy and safety of pitavastatin in children and adolescents with familial hypercholesterolemia in Japan and europe, J. Atherosclerosis Thromb. 25 (2018) 422–429.

[33] J. Besseling, G.K. Hovingh, R. Huijgen, et al., Statins in familial hypercholesterolemia: consequences for coronary artery disease and all-cause mortality, J. Am. Coll. Cardiol. 68 (2016) 252–260.

[34] A.M. Galema-Boers, M.J. Lenzen, S.R. Engelkes, et al., Cardiovascular risk in patients with familial hypercholesterolemia using optimal lipid-lowering therapy, J. Clin. Lipidol. 12 (2018) 409–416.

[35] R. Alonso, E. Andres, N. Mata, et al., Lipoprotein(a) levels in familial hypercholesterolemia: an important predictor of cardiovascular disease independent of the type of LDL receptor mutation, J. Am. Coll. Cardiol. 63 (2014) 1982–1989.

[36] M.S. Nenseter, H.W. Lindvig, T. Ueland, et al., Lipoprotein(a) levels in coronary heart disease-susceptible and -resistant patients with familial hypercholesterolemia, Atherosclerosis 216 (2011) 426–432.

[37] G.K. Hovingh, M.H. Davidson, J.J. Kastelein, et al., Diagnosis and treatment of familial hypercholesterolaemia, Eur. Heart J. 34 (2013) 962–971.

[38] C.P. Cannon, M.A. Blazing, R.P. Giugliano, et al., Ezetimibe added to statin therapy after acute coronary syndromes, N. Engl. J. Med. 372 (2015) 2387–2397.

[39] J.J. Kastelein, F. Akdim, E.S. Stroes, et al., Simvastatin with or without ezetimibe in familial hypercholesterolemia, N. Engl. J. Med. 358 (2008) 1431–1443.

[40] M. Kalogirou, V. Tsimihodimos, M. Elisaf, Pleiotropic effects of ezetimibe: do they really exist? Eur. J. Pharmacol. 633 (2010) 62–70.

[41] G. Avellone, V. Di Garbo, V. Guarnotta, et al., Efficacy and safety of long-term ezetimibe/simvastatin treatment in patients with familial hypercholesterolemia, Int. Angiol. 29 (2010) 514–524.

[42] K. Tsujita, S. Sugiyama, H. Sumida, et al., Impact of dual lipid-lowering strategy with ezetimibe and atorvastatin on coronary plaque regression in patients with percutaneous coronary intervention: the multicenter randomized controlled PRECISE-IVUS trial, J. Am. Coll. Cardiol. 66 (2015) 495–507.

[43] L. Pisciotta, T. Fasano, A. Bellocchio, et al., Effect of ezetimibe coadministered with statins in genotype-confirmed heterozygous FH patients, Atherosclerosis 194 (2007) e116-122.

[44] C. Gagne, D. Gaudet, E. Bruckert, Efficacy and safety of ezetimibe coadministered with atorvastatin or simvastatin in patients with homozygous familial hypercholesterolemia, Circulation 105 (2002) 2469–2475.

[45] A. van der Graaf, C. Cuffie-Jackson, M.N. Vissers, et al., Efficacy and safety of coadministration of ezetimibe and simvastatin in adolescents with heterozygous familial hypercholesterolemia, J. Am. Coll. Cardiol. 52 (2008) 1421–1429.

[46] M. Abifadel, M. Varret, J.P. Rabes, et al., Mutations in PCSK9 cause autosomal dominant hypercholesterolemia, Nat. Genet. 34 (2003) 154–156.

[47] J. Davignon, G. Dubuc, N.G. Seidah, The influence of PCSK9 polymorphisms on serum low-density lipoprotein cholesterol and risk of atherosclerosis, Curr. Atherosclerosis Rep. 12 (2010) 308–315.

[48] J.C. Cohen, E. Boerwinkle, T.H. Mosley Jr., et al., Sequence variations in PCSK9, low LDL, and protection against coronary heart disease, N. Engl. J. Med. 354 (2006) 1264–1272.

[49] M. Benn, B.G. Nordestgaard, P. Grande, et al., PCSK9 R46L, low-density lipoprotein cholesterol levels, and risk of ischemic heart disease: 3 independent studies and meta-analyses, J. Am. Coll. Cardiol. 55 (2010) 2833–2842.

[50] F. Raal, R. Scott, R. Somaratne, 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 (2012) 2408–2417.
[51] F.J. Raal, E.A. Stein, R. Dufour, et al., PCSK9 inhibition with evolocumab (AMG 145) in heterozygous familial hypercholesterolaemia (RUTHERFORD-2): a randomised, double-blind, placebo-controlled trial, Lancet 385 (2015) 331–340.
[52] E.A. Stein, N. Honarpour, S.M. Wasserman, et al., Effect of the proprotein convertase subtilisin/kexin 9 monoclonal antibody, AMG 145, in homozygous familial hypercholesterolemia, Circulation 128 (2013) 2113–2120.
[53] F.J. Raal, N. Honarpour, D.J. Blom, et al., Inhibition of PCSK9 with evolocumab in homozygous familial hypercholesterolaemia (TESLA Part B): a randomised, double-blind, placebo-controlled trial, Lancet 385 (2015) 341–350.
[54] A. Thedrez, D.J. Blom, S. Ramin-Mangata, et al., Homozygous familial hypercholesterolemia patients with identical mutations variably express the LDLR (Low-Density lipoprotein receptor): implications for the efficacy of evolocumab, Arterioscler. Thromb. Vasc. Biol. 38 (2018) 592–598.
[55] E.A. Stein, T. Sampietro, R.D. Santos, et al., Long-term treatment with evolocumab homozygous familial hypercholesterolemia patients: results from the trial assessing long-term use of PCSK9 inhibition in subjects with genetic LDL disorders (TAUSSIG), Atherosclerosis 252 (2016) e44.
[56] F. Raal, C. Kurtz, N. Honarpour, et al., Cardiovascular event rates in homozygous familial hypercholesterolemia (HOFH): trialassessing long-term use of pcsk9 inhibition in subjects with genetic LDL disorders (TAUSSIG) study interim results, Atherosclerosis 252 (2016) e232.
[57] J.J. Kastelein, H.N. Ginsberg, G. Langslet, et al., ODYSSEY FH I and FH II: 78 week results with alirocumab treatment in 735 patients with heterozygous familial hypercholesterolaemia, Eur. Heart J. 36 (2015) 2996–3003.
[58] H.N. Ginsberg, D.J. Rader, F.J. Raal, et al., Efficacy and safety of alirocumab in patients with heterozygous familial hypercholesterolemia and LDL-C of 160 mg/dl or higher, Cardiovasc. Drugs Ther. 30 (2016) 473–483.
[59] P.M. Moriarty, K.G. Parhofer, S.P. Babirak, et al., Alirocumab in patients with heterozygous familial hypercholesterolaemia undergoing lipoprotein apheresis: the ODYSSEY ESCAPE trial, Eur. Heart J. 37 (2016) 3588–3595.
[60] J.G. Robinson, M. Farnier, M. Krempf, et al., Efficacy and safety of alirocumab in reducing lipids and cardiovascular events, N. Engl. J. Med. 372 (2015) 1489–1499.
[61] J.C. Defesche, C. Stefanutti, G. Langslet, et al., Efficacy of alirocumab in 1191 patients with a wide spectrum of mutations in genes causative for familial hypercholesterolemia, J. Clin. Lipidol. 11 (2017), e1337, 1338–1346.
[62] M.L. Hartgers, J.C. Defesche, G. Langslet, et al., Alirocumab efficacy in patients with double heterozygous, compound heterozygous, or homozygous familial hypercholesterolemia, J. Clin. Lipidol. 12 (2018) 390–396.
[63] A.L. Catapano, A. Pirillo, G.D. Norata, Anti-PCSK9 antibodies for the treatment of heterozygous familial hypercholesterolemia: patient selection and perspectives, Vasc. Health Risk Manag. 13 (2017) 343–351.
[64] S.T. Crooke, R.S. Geary, Clinical pharmacological properties of mipomersen (Kynamro), a second generation antisense inhibitor of apolipoprotein B, Br. J. Clin. Pharmacol. 76 (2013) 269–276.
[65] R.S. Geary, B.F. Baker, S.T. Crooke, Clinical and preclinical pharmacokinetics and pharmacodynamics of mipomersen (kynamro((R))): a second-generation antisense oligonucleotide inhibitor of apolipoprotein B, Clin. Pharmacokinet. 54 (2015) 133–146.
[66] F.J. Raal, R.D. Santos, D.J. Blom, 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 375 (2010) 998–1006.
[67] R.D. Santos, P.B. Duell, C. East, et al., Long-term efficacy and safety of mipomersen in patients with familial hypercholesterolaemia: 2-year interim results of an open-label extension, Eur. Heart J. 36 (2015) 566–575.
[68] F. Akdim, M.E. Visser, D.L. Tribble, et al., Effect of mipomersen, an apolipoprotein B synthesis inhibitor, on low-density lipoprotein cholesterol in patients with familial hypercholesterolemia, Am. J. Cardiol. 105 (2010) 1413–1419.
[69] E.A. Stein, R. Dufour, C. Gagne, 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 (2012) 2283–2292.
[70] N. Li, Q. Li, X.Q. Tian, et al., Mipomersen is a promising therapy in the management of hypercholesterolemia: a meta-analysis of randomized controlled trials, Am. J. Cardiovasc. Drugs 14 (2014) 367–376.
[71] R. Panta, K. Dahal, S. Kunwar, Efficacy and safety of mipomersen in treatment of dyslipidemia: a meta-analysis of randomized controlled trials, J. Clin. Lipidol. 9 (2015) 217–225.
[72] M.E. Visser, F. Akdim, D.L. Tribble, et al., Effect of apolipoprotein-B synthesis inhibition on liver triglyceride content in patients with familial hypercholesterolemia, J. Lipid Res. 51 (2010) 1057–1062.
[73] N. Hashemi, R.D. Odze, M.P. McGowan, et al., Liver histology during Mipomersen therapy for severe hypercholesterolemia, J. Clin. Lipidol. 8 (2014) 606–611.
[74] A. Sahebkar, G.F. Watts, New LDL-cholesterol lowering therapies: pharmacology, clinical trials, and relevance to acute coronary syndromes, Clin. Therapeut. 35 (2013) 1082–1098.
[75] P.P. Toth, Emerging LDL therapies: mipomersen-antisense oligonucleotide therapy in the management of hypercholesterolemia, J. Clin. Lipidol. 7 (2013) S6–S10.
[76] P.B. Duell, R.D. Santos, B.A. Kirwan, et al., Long-term mipomersen treatment is associated with a reduction in cardiovascular events in patients with familial hypercholesterolemia, J. Clin. Lipidol. 10 (2016) 1011–1021.
[77] A.J. Hooper, J.R. Burnett, G.F. Watts, Contemporary aspects of the biology and therapeutic regulation of the microsomal triglyceride transfer protein, Circ. Res. 116 (2015) 193–205.
[78] A.C. Goldberg, Emerging low-density lipoprotein therapies: microsomal triglyceride transfer protein inhibitors, J. Clin. Lipidol. 7 (2013) S16–S20.
[79] A.J. Berberich, R.A. Hegele, Lomitapide for the treatment of hypercholesterolemia, Expet Opin. Pharmacother. 18 (2017) 1261–1268.
[80] M. Cuchel, L.T. Bloedon, P.O. Szapary, et al., Inhibition of microsomal triglyceride transfer protein in familial hypercholesterolemia, N. Engl. J. Med. 356 (2007) 148–156.
[81] M. Averna, A.B. Cefalu, C. Stefanutti, et al., Individual analysis of patients with HoFH participating in a phase 3 trial with lomitapide: the Italian cohort, Nutr. Metabol. Cardiovasc. Dis. : Nutr. Metabol. Cardiovasc. Dis. 26 (2016) 36–44.
[82] S. Tuteja, D. Duffy, R.L. Dunbar, et al., Pharmacokinetic interactions of the microsomal triglyceride transfer protein inhibitor, lomitapide, with drugs commonly used in the management of hypercholesterolemia, Pharmacotherapy 34 (2014) 227–239.
[83] http://www.aegerion.com/Collateral/Documents/English-US/012187_JuxtapidPI_8%205x11_FIN.pdf.
[84] M. Cuchel, E.A. Meagher, H. du Toit Theron, 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 (2013) 40–46.
[85] D.J. Blom, M.R. Averna, E.A. Meagher, et al., Long-term efficacy and safety of the microsomal triglyceride transfer protein inhibitor lomitapide in patients with homozygous familial hypercholesterolemia, Circulation 136 (2017) 332–335.
[86] D.J. Blom, Z.A. Fayad, J.J. Kastelein, et al., LOWER, a registry of lomitapide-treated patients with homozygous familial hypercholesterolemia: rationale and design, J. Clin. Lipidol. 10 (2016) 273–282.
[87] W.V. Brown, D.A. Bramlet, J.L. Ross, et al., JCL roundtable: risk evaluation and mitigation strategy, J. Clin. Lipidol. 10 (2016) 1288–1296.
[88] C. Stefanutti, U. Julius, G.F. Watts, et al., Toward an international consensus-Integrating lipoprotein apheresis and new lipid-lowering drugs, J. Clin. Lipidol. 11 (2017) 858–871 e853.
[89] A. Alim, Y. Tokat, Y. Erdogan, et al., Liver transplantation for homozygote familial hypercholesterolemia: the only curative treatment, Pediatr. Transplant. 20 (2016) 1060–1064.
[90] M. Mansoorian, K. Kazemi, S. Nikeghbalian, et al., Liver transplantation as a definitive treatment for familial hypercholesterolemia: a series of 36 cases, Pediatr. Transplant. 19 (2015) 605–611.
[91] M.M. Page, E.I. Ekinci, R.M. Jones, et al., Liver transplantation for the treatment of homozygous familial hypercholesterolaemia in an era of emerging lipid-lowering therapies, Intern. Med. J. 44 (2014) 601–604.
[92] M. Greco, J.D. Robinson, O. Eltayeb, et al., Progressive aortic stenosis in homozygous familial hypercholesterolemia after liver transplant, Pediatrics (2016) 138.
[93] M. Ibrahim, I. El-Hamamsy, M. Barbir, et al., Translational lessons from a case of combined heart and liver transplantation for familial hypercholesterolemia 20 years post-operatively, J Cardiovasc Transl Res 5 (2012) 351–358.
[94] K. Fitzgerald, S. White, A. Borodovsky, et al., A highly durable RNAi therapeutic inhibitor of PCSK9, N. Engl. J. Med. 376 (2017) 41–51.
[95] K.K. Ray, U. Landmesser, L.A. Leiter, et al., Inclisiran in patients at high cardiovascular risk with elevated LDL cholesterol, N. Engl. J. Med. 376 (2017) 1430–1440.
[96] N.O. Stitziel, A.V. Khera, X. Wang, et al., ANGPTL3 deficiency and protection against coronary artery disease, J. Am. Coll. Cardiol. 69 (2017) 2054–2063.
[97] Y. Wang, V. Gusarova, S. Banfi, et al., Inactivation of ANGPTL3 reduces hepatic VLDL-triglyceride secretion, J. Lipid Res. 56 (2015) 1296–1307.
[98] D. Gaudet, D.A. Gipe, R. Pordy, et al., ANGPTL3 inhibition in homozygous familial hypercholesterolemia, N. Engl. J. Med. 377 (2017) 296–297.
[99] http://globenewswire.com/news-release/2018/03/07/1417477/0/en/Esperion-Announces-Positive-Top-Line-Results-from-First-Pivotal-Phase-3-Study-of-Bempedoic-Acid.html.
[100] E. Ajufo, M. Cuchel, Recent developments in gene therapy for homozygous familial hypercholesterolemia, Curr. Atherosclerosis Rep. 18 (2016) 22.
[101] E. Stein, H. Bays, M. Koren, et al., Efficacy and safety of gemcabene as add-on to stable statin therapy in hypercholesterolemic patients, J. Clin. Lipidol. 10 (2016) 1212–1222.
[102] https://globenewswire.com/news-release/2017/06/28/1031562/0/en/Gemphire-Announces-Top-Line-Data-from-COBALT-1-Phase-2b-Clinical-Trial-in-HoFH-Patients.html.
[103] https://globenewswire.com/news-release/2017/08/07/1080946/0/en/Gemphire-Announces-Top-Line-Data-from-ROYAL-1-Phase-2b-Clinical-Trial-in-Hypercholesterolemic-Patients.html.
[104] A. Neil, J. Cooper, J. Betteridge, 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 (2008) 2625–2633.
[105] B. Starr, S.G. Hadfield, B.A. Hutten, et al., Development of sensitive and

specific age- and gender-specific low-density lipoprotein cholesterol cutoffs for diagnosis of first-degree relatives with familial hypercholesterolaemia in cascade testing, Clin. Chem. Lab. Med. 46 (2008) 791–803.
[106] L.J. Mundal, J. Igland, M.B. Veierod, et al., Impact of age on excess risk of coronary heart disease in patients with familial hypercholesterolaemia, Heart (2018 Apr 5), https://doi.org/10.1136/heartjnl-2017-312706 pii: heartjnl-2017-312706.
[107] Institute of Medicine, Promoting Cardiovascular Health in the Developing World: a Critical Challenge to Achieve Global Health, The National Academies Press, Washington, DC, 2010. https://doi.org/10.17226/12815.
[108] S. Li, N.Q. Wu, C.G. Zhu, et al., Significance of lipoprotein(a) levels in familial hypercholesterolemia and coronary artery disease, Atherosclerosis 260 (2017) 67–74.
[109] B.G. Nordestgaard, M.J. Chapman, K. Ray, et al., Lipoprotein(a) as a cardiovascular risk factor: current status, Eur. Heart J. 31 (2010) 2844–2853.
[110] S. Tonstad, O. Joakimsen, E. Stensland-Bugge, et al., Carotid intima-media thickness and plaque in patients with familial hypercholesterolaemia mutations and control subjects, Eur. J. Clin. Invest. 28 (1998) 971–979.