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STATE-OF-THE-ART PAPER

The Severe Hypercholesterolemia Phenotype

Clinical Diagnosis, Management, and Emerging Therapies

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The severe hypercholesterolemia phenotype includes all patients with marked elevation of low-density lipoprotein cholesterol (LDL-C) levels. The most common cause is autosomal dominant hypercholesterolemia, an inherited disorder caused by mutations either in *LDL receptor*, apolipoprotein B (*APOB*), or proprotein convertase subtilisin kexin type 9 (*PCSK9*) genes. However, it is now known that many subjects with severe inherited hypercholesterolemia have no defects in these genes. These cases are caused either by mutations in genes yet to be identified or are consequences of polygenic, epigenetic, or acquired defects. Because the clinical consequences of extreme hypercholesterolemia are the same no matter the cause, the focus should be on the identification of subjects with severe hypercholesterolemia, followed by phenotypic screening of family members. Genetic screening is not necessary to diagnose or initiate treatment for the severe hypercholesterolemia phenotype. Management of severe hypercholesterolemia is based on risk factor modification and use of multiple lipid-lowering medications. Lipoprotein apheresis is indicated for coronary artery disease (CAD) patients taking maximally tolerated therapy and with LDL-C levels >200 mg/dl (>300 mg/dl if without CAD). A microsomal triglyceride transfer protein inhibitor and an antisense oligonucleotide against APOB have recently been approved for use in subjects with clinically diagnosed homozygous familial hypercholesterolemia. PCSK9 inhibitors, currently in phase II and III trials, lower LDL-C up to an additional 70% in the setting of maximally tolerated medical therapy and have the potential to reduce LDL-C to <70 mg/dl in most patients. Early identification of affected individuals and aggressive treatment should significantly reduce the burden of cardiovascular disease in society. (J Am Coll Cardiol 2014;63:1935–47)

The severe hypercholesterolemia phenotype includes all subjects with low-density lipoprotein cholesterol (LDL-C) levels above 190 mg/dl, regardless of the cause. The term autosomal dominant hypercholesterolemia (ADH) is reserved for patients with mutations in genes controlling LDL levels. Familial hypercholesterolemia (FH) is a common monogenic disorder caused by abnormalities in the LDL receptor (LDLR) protein, commonly inherited in a codominant fashion (1). Patients can be true FH homozygotes (HoFH), with 2 identical mutations; compound heterozygotes, with a different mutation in each allele; or FH heterozygotes (HeFH), with only one mutated allele. ADH includes FH and the hypercholesterolemia resulting from defects in 2 other major genes, *APOB* and *PCSK9*, which influence plasma LDL clearance by affecting the efficiency of ligand–receptor interaction. The inadequate LDL clearance manifested in all forms of ADH leads to marked elevations of plasma LDL-C levels and premature cardiovascular disease (CVD) (2). In individuals with true HoFH, the LDLR pathway is nonfunctional or markedly defective (2% to 30% activity), leading to plasma LDL-C levels 4 to 8 times above average (>500 mg/dl), whereas in patients with HeFH, the loss in receptor activity (up to 50%) leads to LDL-C levels 2 to 3 times above average (3). Many individuals with LDL-C >190 mg/dl do not have defects in any of the 3 genes. A polygenic origin is likely in many of these cases (4), and thus, genetic screening strategies are not easily endorsable as they pose great challenges to comprehensive, effective, and economical implementation. Because the risk of vascular disease is determined by lifelong exposure to hypercholesterolemia, not by the genotype that produces it, we propose that screening should focus on identifying subjects with the phenotype without investing resources in the identification of the genetic causes, as also suggested in a recent editorial by Stein and Raal (5).

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Abbreviations and Acronyms

ADH = autosomal dominant hypercholesterolemia

APOB = apolipoprotein B

CAD = coronary artery disease

CHD = coronary heart disease

FH = familial hypercholesterolemia

HeFH = heterozygous familial hypercholesterolemia

HoFH = homozygous familial hypercholesterolemia

LDL-C = low-density lipoprotein cholesterol

LDLR = low-density lipoprotein receptor

Lp(a) = lipoprotein(a)

This review summarizes the state-of-the-art in the identification of subjects with the severe hypercholesterolemia phenotype and ADH, screening of affected family members, and established and emerging treatments.

Prevalence of Severe Hypercholesterolemia Phenotype and Risk of CHD

Approximately 600,000 people in the United States and between 14 and 35 million people worldwide manifest the severe hypercholesterolemia phenotype (2,6). HeFH is estimated to occur in 1 of every 200 to 500 persons, with approximately 10 million affected worldwide, and the frequency may vary among certain populations because of gene founder effects. True HoFH is rare, with a supposed prevalence of approximately 1 per 1,000,000 persons.

The risk of premature coronary heart disease (CHD) is estimated to be approximately 20-fold higher in untreated FH patients than in control subjects (Fig. 1) (7). Fatal or nonfatal coronary events occur in approximately 50% of males before age 50 and 30% of females before age 60. In subjects with HoFH, sudden death, acute myocardial infarction (MI), or need for revascularization may occur in patients in the first decade of life (8,9). HoFH also commonly causes aortic stenosis, both valvular and supravalvular, due to lipid deposition in the aortic valve leaflets and aortic root (10). The prevalence of HeFH is higher among patients with MI, from ~5% of patients <60 years of age to almost 20% in patients <45 years of age (11–13). Additional risk factors such as smoking, hypertension, diabetes, male sex, and low HDL-C (14) further amplify CHD risk by 2- to 3-fold (15). In addition, elevated lipoprotein (a) (Lp[a]) levels are common in FH patients, and the trait seems to be a consequence of FH and is not inherited separately (16,17). Given that the evidence to date does not suggest that the LDLR is involved in Lp(a) clearance (18,19) this suggests that overproduction of APOB, known to occur in FH (20–23), may be partially responsible for the overproduction of Lp(a) particles.

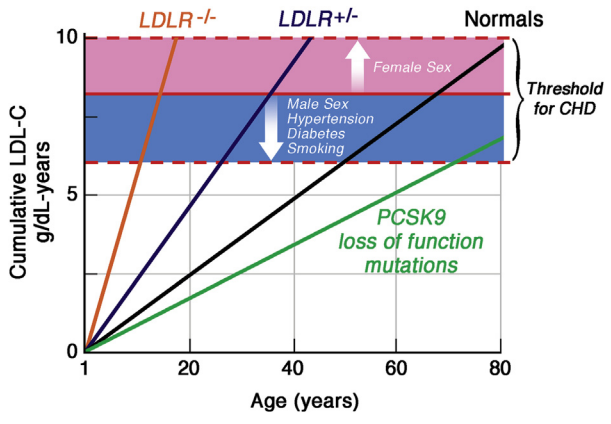

Figure 1 Relationship Between Age and Cumulative LDL-C Exposure

Coronary heart disease (CHD) risk is estimated for homozygous familial hypercholesterolemia (HoFH), heterozygous familial hypercholesterolemia (HeFH), and age-adjusted low-density lipoprotein cholesterol (LDL-C) levels in normal individuals. The **horizontal red line** represents a theoretical threshold of the cumulative LDL-C exposure required for development of CHD. The **height of the red line** will be lower in the presence of additional CHD risk factors. Reprinted with permission from Horton et al. (7).

Genetics

Our physiological understanding of FH is based on the pioneering work of Brown and Goldstein (1), who established a molecular link among defects in the *LDLR* gene, loss of function of LDLR, the cell surface protein that binds and internalizes LDL particles, and the inherited hypercholesterolemic trait (1). Although classic FH is still defined as severe hypercholesterolemia caused by a defect in the LDLR, a functionally similar effect is caused by mutations in *APOB* (the ligand for LDLR) or PCSK9 (the terminator of LDLR lifecycle) (Fig. 2, Table 1) (24,25), all of which significantly impair the function of the LDLR pathway. Mutations in LDLR are responsible for approximately 85% to 90% of cases of clinical FH, and >1,600 mutations have been documented to date (26). Common mutations in the *LDLR* gene include deletions, insertions, and missense and nonsense changes affecting all of the major steps in LDLR trafficking and function (Fig. 3) (reviewed in Hopkins et al. [2]). A less common mutation in APOB leading to poor interaction with the LDLR (27) is responsible for a phenotype indistinguishable from classic FH, except for less drastic elevations in LDL-C. Additionally, ultrarare monogenic defects can cause severe autosomal recessive hypercholesterolemia, caused by defects in a liver-specific LDLR chaperone LDLR adaptor-related protein 1 (LDLRAP1) (28) and beta-sitosterolemia due to the abnormal intestinal absorption of plant sterols (29), both of which are recessively inherited.

PCSK9 is a secreted convertase that binds to the LDLR and targets it for lysosomal degradation mostly in the hepatocyte. Gain-of-function mutations in PCSK9 leading to elevated plasma LDL-C levels are an uncommon cause of FH (30). Interestingly, subjects with loss-of-function mutations in PCSK9 have reduced plasma levels of LDL-C and are significantly protected from coronary heart disease (CAD) (31). Indeed, the extent of protection is

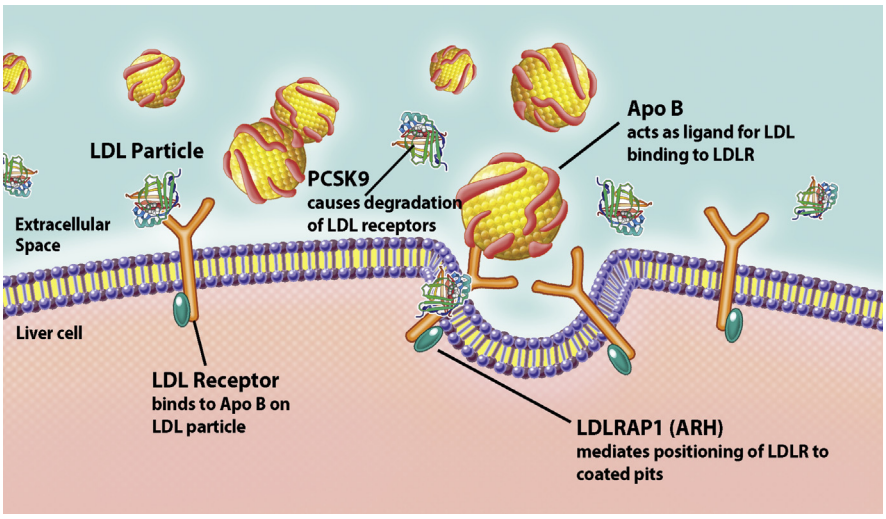

Figure 2 Major Molecular Causes of Familial Hypercholesterolemia

The severe hypercholesterolemia phenotype is caused predominantly by defects in the low-density lipoprotein receptor (LDLR) APOB-100 and PCSK9 (when dominantly inherited) and by defects in the liver-specific LDLR adaptor-related protein 1 (LDLRAP1), a chaperone for proper positioning of LDLR on the vascular side of the plasma membrane (when recessively inherited).

disproportionately large relative to the degree of LDL-C lowering, which suggests that a lifelong low LDL-C is a powerful determinant of low CVD risk (Fig. 4).

Although our knowledge of the mechanisms and critical proteins in the LDL cycle seems to be complete, it has been frequently reported that 30% to 50% of subjects with a classic phenotypic presentation of FH have no defects in any of the culprit genes (32). Thus, multiple genotypes may produce the FH phenotype, and a phenotypic diagnosis of FH is not equivalent to diagnosing a monogenic error in the LDLR pathway (Table 1). In particular, the demonstration that many individuals with apparent FH have a polygenic origin to their phenotype (4) has transformed our understanding of the genetic architecture of this disease. In polygenic FH, involvement of family members should be substantially less common than in classic FH, thus reducing the efficacy and cost effectiveness of family screening strategies. Therefore, for practical purposes, FH should be diagnosed at the phenotypic level to avoid the indefensible position that only real monogenic FH warrants aggressive intervention. In addition, genetic screening has the potential to identify "causal" mutations in carriers who, for unclear reasons, have low LDL-C levels and therefore do not qualify for therapy. In other words, the phenotype is not the invariable product of the genotype.

Table 1 Genetic Causes of Familial Hypercholesterolemia Phenotypes

I. Molecular Defects in the Low-Density Lipoprotein Receptor Pathway
• Deletion, missense, nonsense, and insertion mutations in low-density lipoprotein receptor *(LDLR)* affecting receptor function (>1,600 mutations reported to date);
• Mutations in apolipoprotein B *(APOB)* that affect the ability of the ligand to recognize LDLR (most commonly a single base change at position 3,500);
• Gain-of-function mutations in *PCSK9* causing a reduction in *LDLR* on the cell surface;
• Mutations in *LDLR* accessory protein 1 (LDLRAP1) causing improper placement of LDLR on the hepatocyte membrane (a rare and recessively inherited form).
II. Polygenic Hypercholesterolemia
III. Other Monogenic, Epigenetic, and Nongenetic Forms (yet to be discovered)

Pathophysiology

The liver is the final destination for most LDL particles, which are extracted from plasma either by the LDLR or by nonspecific pathways (33,34). Uptake by the LDLR is based on the specific binding of APOB to the LDLR, internalization of the receptor–ligand complex, targeting of the LDL ligand to the lysosome, and recycling of LDLR to the cell surface. PCSK9 and inducible degrader of LDL (IDOL), an E3 ubiquitin ligase, modulate LDL uptake by the LDLR (30,35) but do not affect the nonspecific pathways. Even though LDL particles bind with high affinity to the LDLR, this pathway has a low absolute transport capacity, and therefore, the nonspecific pathways for LDL clearance are always operational, even for LDL-C levels approximately 30 mg/dl (11,33). These pathways are not saturable and therefore present no absolute limit on the number of LDL particles that can be removed per day (34). Therefore, the higher the plasma LDL-C level, the greater the relative and absolute proportions of LDL particles that are cleared by the nonspecific pathways (36).

In HeFH, transport through the LDL pathway is reduced by up to 50%, but absolute hepatic LDL particle

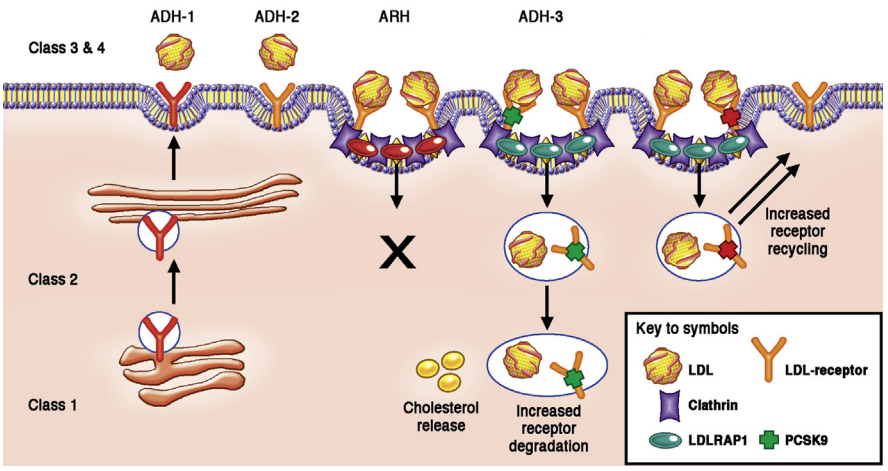

Figure 3 Cellular Processes Mediating LDL Uptake and Causing Familial Hypercholesterolemia

Five major classes of *LDLR* mutations cause familial hypercholesterolemia (or autosomal dominant hypercholesterolemia [ADH]). In ADH-1, the mutations prevent (i) production of immunologically detectable protein; (ii) ER exit of complete (a) or partial (b) gene-encoded products; (iii) binding of apolipoprotein B-100 (APOB-100) (a) and apoE (b) ligands; (iv) constitutive endocytosis, including of low-density lipoprotein receptor (LDLR)-APOB-100 (a) and of very-low-density lipoprotein (VLDL)-apoE (b); and (v) release of internalized LDLR ligand (not shown for clarity). ADH-2 is caused by *APOB* mutations that block the binding of APOB-100 to the LDLR. ADH-3 is caused by gain-of-function *PCSK9* mutations. **Red**, loss-of-function mutation; **green**, gain-of-function mutation. Reprinted with permission from Calandra et al. (25).

uptake is not reduced. On the contrary, total LDL-C clearance from plasma is doubled in HeFH and is 4 times normal in oFH (37). To avoid accumulation within the hepatocyte, this excess cholesterol is exported within the APOB-containing lipoprotein, transferred to HDL, excreted in the bile, or transformed into bile acids. Hepatic cholesterol

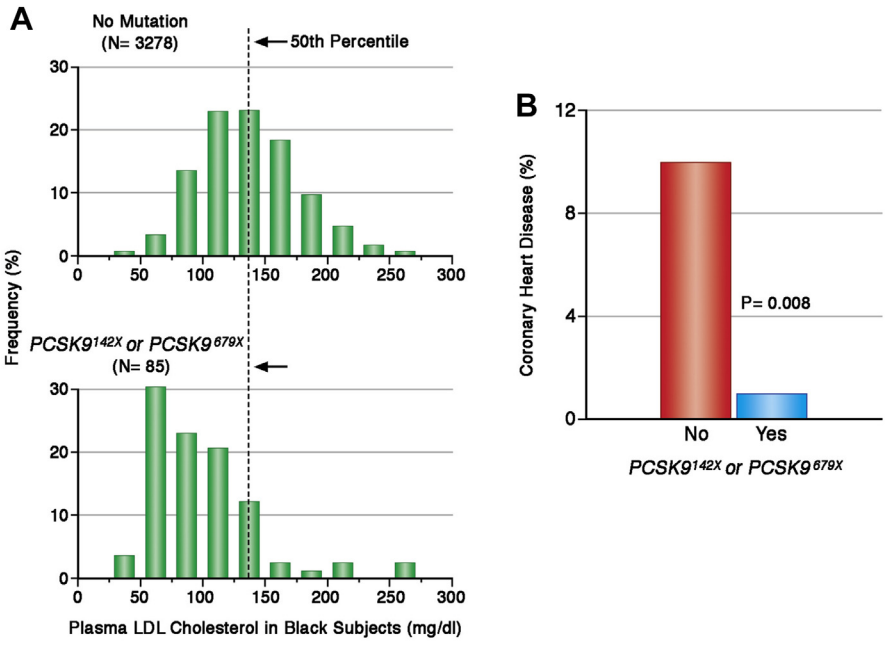

Figure 4 Role of PCSK9 in Risk of CAD

(A) Distribution of plasma low-density lipoprotein cholesterol (LDL-C) levels at baseline among 3,278 black subjects who did not have a *PCSK9142X* or *PCSK9679X* allele **(top)** is compared with the distribution of levels among the 85 black subjects who did have 1 of these two alleles **(bottom)**. **(B)** Percentage of participants from these 2 groups who had no evidence of coronary heart disease at baseline and in whom coronary heart disease developed during the 15-year follow-up period. To convert values for LDL-C to millimoles per liter, multiply by 0.02586. Reprinted with permission from Cohen et al. (31).

homeostasis is, therefore, partly maintained by the APOB lipoprotein transport system (16), as suggested by the evidence that secretion of APOB lipoproteins is increased in FH (38–41). Any increase in LDL production will produce a disproportionate increase in plasma LDL-C because the additional LDL particles are cleared through inefficient pathways. Even in subjects with normal LDLR function, increases in LDL production will raise LDL-C levels above normal. In fact, increased production, rather than decreased clearance, may be the most common cause of elevated LDL-C (42). Reducing secretion of hepatic APOB lipoproteins is, therefore, a physiologically appropriate target to reduce LDL-C in patients with FH.

Clinical Diagnosis

FH is clinically diagnosed by 5 major criteria including family history of premature CAD, presence of early CAD in the index case, elevated LDL-C, tendon xanthomas, and corneal arcus. HeFH can be suspected when LDL-C is ≥190 mg/dl in adults and ≥160 mg/dl in children. HoFH should be suspected for LDL-C levels >400 mg/dl (2). Secondary causes of hypercholesterolemia such as hypothyroidism, nephrotic syndrome, and liver disease should be ruled out. FH is more likely in individuals with a positive family history of CAD (before age 55 in men, age 65 in women), when 2 or more first-degree relatives have elevated LDL-C or when pediatric cases are identified. Xanthomas in the Achilles and finger extensor tendons at any age are found in approximately 30% to 40% of adults with FH. Corneal arcus in patients younger than 45 is an insensitive but specific finding. Causative mutations affecting LDL-C levels are diagnostic, even in the absence of other criteria. Patients with FH commonly have markedly elevated LDL-C, normal triglyceride levels, and reduced high-density lipoprotein cholesterol (HDL-C). Low HDL and loss of HDL function may be contributors to CVD risk in FH subjects (43). Universal lipid screening is recommended in all individuals by age 20 and in children as young as 2 in the presence of family history of premature CVD or severe hypercholesterolemia (44).

Validated algorithms may also assist in the clinical diagnosis of FH, such as those from the Dutch Lipid Clinic Network (45) and Simon-Broome Registry (46) (Online Tables 1 and 2). A downloadable application is also available online (FH diagnosis; KKIT Creations, LLC, Dana Point, California).

Genetic Screening

Genetic screening for FH is not needed for clinical management and not generally covered by medical insurance but is essential to characterize the defect. Identification of a causal mutation may be helpful in improving a patient's compliance with medical therapy, although this has not been proven. Applying the Simon-Broome criteria, the prevalence of mutation-positive patients is 30% among subjects with possible FH and 60% to 80% among those with definite FH. Because most severe hypercholesterolemic patients fall in the range of possible FH, this means that most are mutation-negative and do not display an obvious genetic reason for their lipid phenotype. Importantly, a negative genetic test result does not exclude FH, because many of the clinically definite FH patients will not be found to have a mutation despite an exhaustive search using current methods. The recognition of a polygenic origin for a substantial portion of the FH phenotype has considerably complicated the design and application of any genetic screening strategy (4,5).

Cascade Screening

Cascade screening is the process of systematic family tracing to identify people carrying a genetic condition and is infrequently used in clinical practice, although it is recommended by most guidelines (47). For FH, it is carried out by screening lipid profiles of close relatives of the index patient and is the most cost-effective method of finding new cases of FH. Because LDL-C levels drive clinical risk, and it is difficult for physicians to remember diagnostic criteria for an uncommon disease, we suggest that emphasis be placed on severe hypercholesterolemia and that recognition of a case be sufficient to initiate family screening for other individuals with elevated levels of LDL-C.

Aggressive Lipid Lowering and CVD Outcomes

Aggressive lipid lowering in FH patients has been shown to decrease progression of angiographically determined CAD (48) and to reduce CVD events (49,50). For example, Neil et al. (50) prospectively followed 3,382 patients with HeFH between 1980 and 2006, before and after introduction of statins. CHD mortality was significantly lower among statin users, with a 48% reduction among patients without prior CVD and a 25% reduction in those with established disease. Similar findings were reported (51) from a large cohort from the Netherlands (Fig. 5). Raal et al. (49) retrospectively studied 149 patients with HoFH from 2 specialized lipid clinics in South Africa before and after lipid-lowering therapy. A significant reduction in major adverse cardiovascular events was noted with a hazard ratio for benefit from lipid-lowering therapy of 0.49 ($p < 0.0001$) (Fig. 6), following an absolute reduction in LDL-C from 15.9 ± 3.9 nmol (614.8 ± 150.8 mg/dl) to 11.7 ± 3.4 nmol/l (452.4 ± 131.5 mg/dl) (−26.4%). Although no randomized clinical trials of statin efficacy have been done in HeFH, the 4S (Scandinavian Simvastatin Survival Study) (52), WOSCOPS (West of Scotland Coronary Prevention Study) (53), and LRC-CPPT (Lipid Research Clinics Coronary Primary Prevention Trial) (54) trials

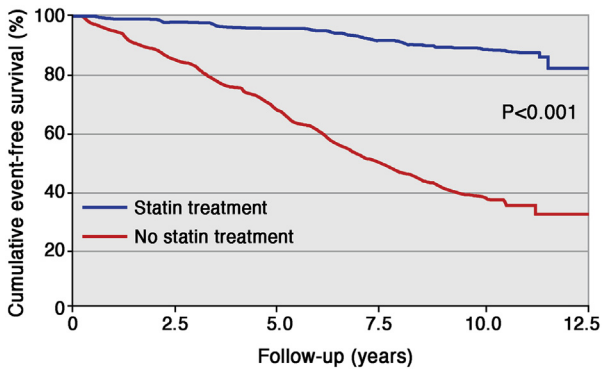

Figure 5 **Coronary Heart Disease Risk of Heterozygous Familial Hypercholesterolemia Patients According to Statin Treatment**

Kaplan-Meier estimates of cumulative coronary heart disease-free survival among patients with familial hypercholesterolemia according to statin treatment. Reprinted with permission from Versmissen et al. (51).

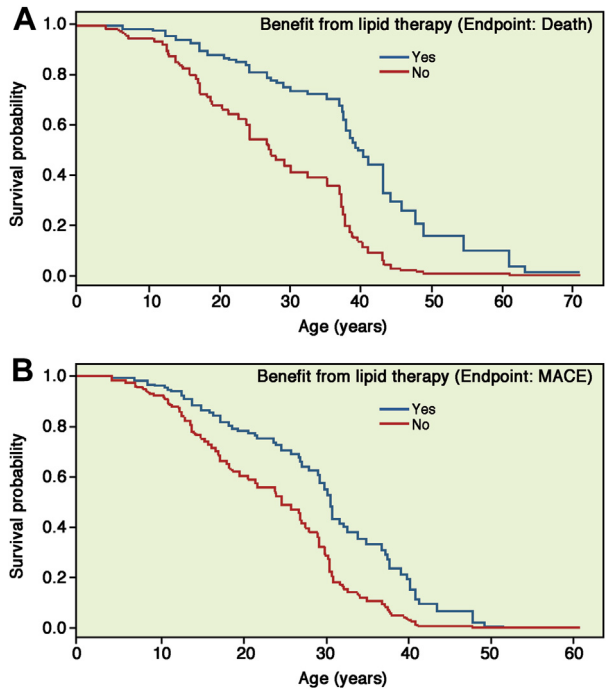

Figure 6 **Coronary Heart Disease Risk of Homozygous Familial Hypercholesterolemia Patients According to Statin Treatment**

Cox proportional hazards model with time-varying benefit from statin therapy comparing treated with untreated person-years for survival **(A)** and first major adverse cardiovascular event (MACE) **(B)** in patients with homozygous familial hypercholesterolemia, with year of birth fixed as the mean year of birth. Reprinted with permission from Raal et al. (49).

were likely enriched in FH patients (mean baseline LDL-C of 189 mg/dl, 192 mg/dl, and 216 mg/dl, respectively), and their results support the contention that LDL-C lowering in patients with FH reduces CHD risk.

Current Therapies for FH

Risk assessment algorithms, such as the Framingham Risk Score, do not apply to FH patients, who are considered a special risk category. In the recently released American Heart Association/American College of Cardiology guidelines, this category would include all those with an LDL-C ≥190 mg/dl (5,55). It is estimated that FH is diagnosed as such in only approximately 20% of patients and that <10% of FH patients reach LDL treatment goals (56). Concomitant with initiation of lipid-lowering medications, patients should be counseled on lifestyle changes, including avoidance of smoking, regular exercise, and adoption of a diet that is low in trans and saturated fats, refined sugars, and cholesterol; is rich in fiber and supplemented with plant sterols; and is calorie-appropriate for body weight management. Diagnosis of FH warrants initiation of drug therapy for LDL-C ≥190 mg/dl in all patients, including children older than 10 (44).

According to the National Lipid Association (57), the goal of treatment for FH patients is a ≥50% reduction in LDL-C, using moderate- to high-dose statin therapy (Fig. 7). A consensus statement of the European Atherosclerosis Society on FH suggested LDL-C targets of <3.5 mmol/l (<135 mg/dl) for children, <2.5 mmol/l (<100 mg/dl) for adults, and <1.8 mmol/l (<70 mg/dl) for adults with known CHD or diabetes (6). Higher risk patients, such as those with prior CVD, comorbidities (diabetes, hypertension), or additional risk factors (smoking, elevated Lp[a] levels) generally need multiple drugs to achieve an LDL-C level <100 mg/dl. Statin monotherapy can decrease LDL-C up to 55% to 60%, but even that is normally not enough to reach LDL-C goal in patients with clinically manifested CHD (58). Ezetimibe, niacin, fibrates, and bile acid sequestrants are treatment options for intensification of therapy or for those intolerant of statins. Combination therapy can lead to an additional LDL-C reduction of 20% to 30% (59–61). Most patients with CVD will require 3 drugs to achieve an LDL-C level <100 mg/dl, whereas an LDL of <70 mg/dl is beyond the reach of most patients with FH.

Lipoprotein apheresis is used when drug therapy is ineffective or not tolerated and is normally performed biweekly for HoFH and for severe HeFH when LDL is above 300 mg/dl (>200 for those with CAD) (62). Lipoprotein apheresis uses either heparin (heparin-induced extracorporeal LDL precipitation or HELP) or dextran sulfate (Liposorber, Kaneka Corporation, New York, New York) to remove APOB-containing lipoproteins from plasma. Apheresis results in 60% to 70% reduction in LDL-C and Lp(a) immediately following the procedure, but levels usually return to baseline in 2 weeks, and the time-averaged

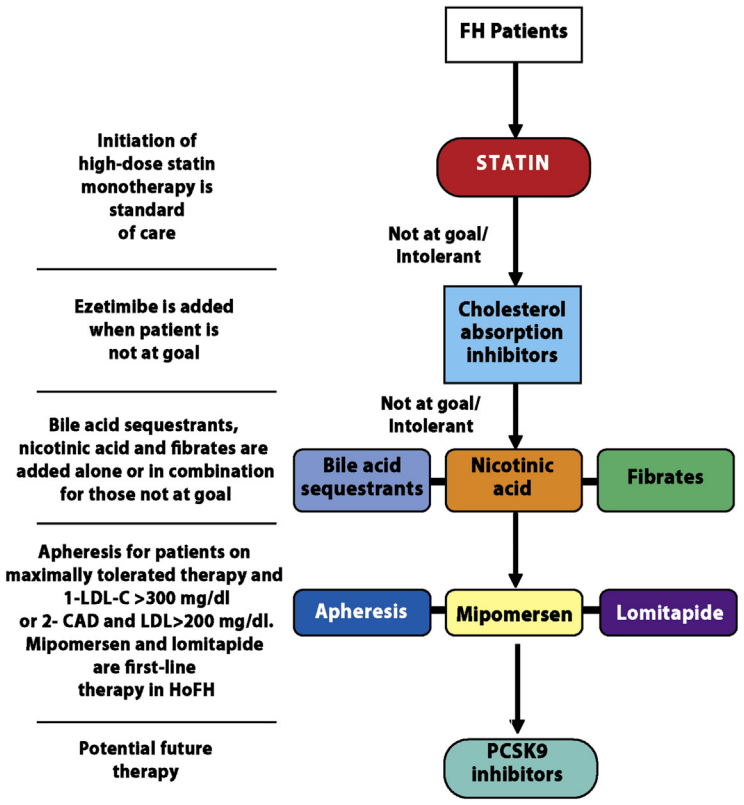

Figure 7 Treatment Algorithm for Patients With Familial Hypercholesterolemia

Adapted with permission from Goldberg et al. (24).

daily LDL-C reduction is equivalent to ~40%. Apheresis also significantly reduces levels of oxidized phospholipids and lipoprotein-associated phospholipase A_2 particles (63). High Lp(a) levels are an approved indication for apheresis in some European countries (64). In the United States, approval is granted on a case-by-case basis. Randomized trials are not feasible with apheresis, but observational studies suggest a significant reduction in events following apheresis compared to the period before apheresis initiation (65,66). A recent study conducted by 1 of the authors of this review showed that lipoprotein apheresis also causes a substantial reduction in plasma PCSK9 levels (67).

Recently Approved Therapies for HoFH

The microsomal triglyceride transfer protein (MTP) inhibitor lomitapide (Juxtapid, Aegerion Pharmaceuticals, Inc., Cambridge, Massachusetts) and the APOB antisense oligonucleotide mipomersen (Kynamro, Genzyme Corporation, Cambridge, Massachusetts) were recently approved by the Food and Drug Administration (FDA) as orphan drugs for LDL-C lowering as an adjunct to diet and other lipid-lowering drugs in patients with HoFH. Lomitapide was also approved by European Medicines Agency, whereas mipomersen was not. The FDA has not defined explicit criteria for the diagnosis of HoFH, and therefore, a clinical diagnosis is needed for initiating therapy, and genetic confirmation is not required. The safety and effectiveness of lomitapide and mipomersen have not been evaluated in patients without HoFH, and these agents' effects on CVD morbidity and mortality is not known. Because of the risk of hepatotoxicity, lomitapide and mipomersen are available only through a Risk Evaluation and Mitigation Strategy (REMS) program, and only certified healthcare providers and pharmacies may prescribe and distribute them. The consequences of lomitapide- and mipomersen-induced aminotransferase elevation and hepatic fat are unknown and should be carefully monitored in practice.

Microsomal triglyceride transfer protein inhibitor lomitapide. Figure 8 describes the process of APOB production and the role of MTP in creating very-low-density lipoprotein (VLDL) particles. MTP is the key protein that delivers the lipid droplet to APOB, crucial for the assembly and secretion of APOB-containing lipoproteins in liver and intestine (68,69). Inhibition of MTP decreases the secretion of chylomicrons and VLDL and also causes reduced production of LDL (68). The published clinical experience includes 35 HoFH patients, age

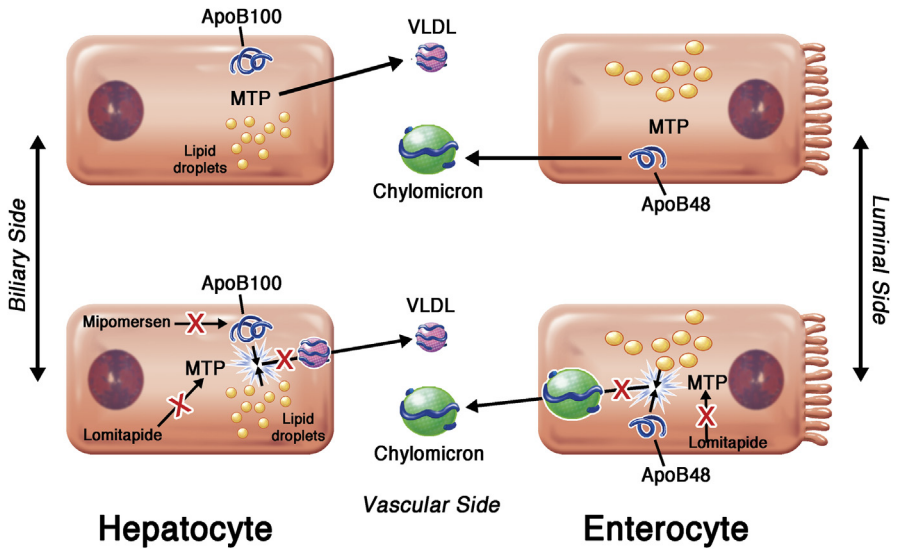

Figure 8 **Lipoprotein Assembly and Secretion from Liver and Intestine**

Effects of lomitapide and mipomersen. **(Top)** Intracellular assembly of triglyceride-rich lipoproteins from the transfer of the lipid droplet (LD) to apolipoprotein B-100 (APOB-100) in the liver **(left)** and APOB-48 in the intestine **(right)** mediated by microsomal triglyceride transfer protein (MTP) and resulting in secretion of very-low-density lipoprotein (VLDL) from hepatocytes and chylomicrons from enterocytes. **(Bottom)** Effects of the newly approved orphan drugs lomitapide and mipomersen. Lomitapide inhibits MTP activity in both liver and intestine, whereas mipomersen stops production of hepatic APOB-100 and has no effect on intestinal lipoprotein production.

>18 years, and mean age of 30.7 ± 10.6 years in 2 studies (70,71), and 84 patients with moderate hypercholesterolemia in another study (72). The main study was a single-arm, open-label trial in which 29 patients with HoFH were treated for 26 weeks with dose escalation from 5 to 60 mg/day and were followed until week 78 for safety assessment. Twenty-three patients completed the full study of a median dose of 40 mg/day, baseline LDL-C of 336 mg/dl, and pre-existing treatment including statins (93%), other lipid drugs (79%), and lipoprotein apheresis (62%). Mean LDL-C was reduced by 50% (to 166 mg/dl) at week 26, 44% (to 197 mg/dl) at week 52, and by 38% (to 208 mg/dl) at week 78 (Fig. 9). Lp(a) levels were reduced by 15% at 26 weeks, but the effect disappeared by 78 weeks. Patients were instructed to eat a low-fat diet (<20% energy) and to take daily fat-soluble vitamins. Five patients (17%) discontinued treatment mainly due to gastrointestinal symptoms of diarrhea and nausea. Four

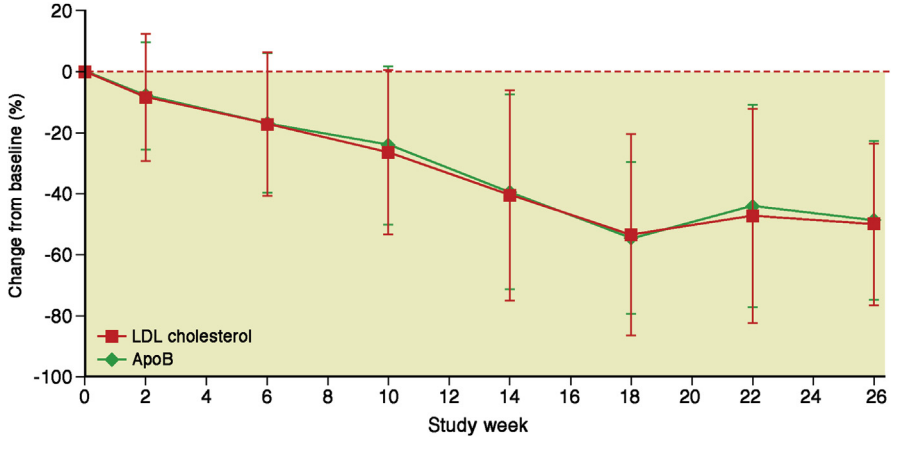

Figure 9 **Effect of Lomitapide on Low-Density Lipoprotein Cholesterol Levels**

Mean percent changes in low-density lipoprotein cholesterol (LDL-C), TC, and apolipoprotein B (APOB) levels from baseline to week 26 following treatment with lomitapide. Reprinted with permission from Cuchel et al. (71).

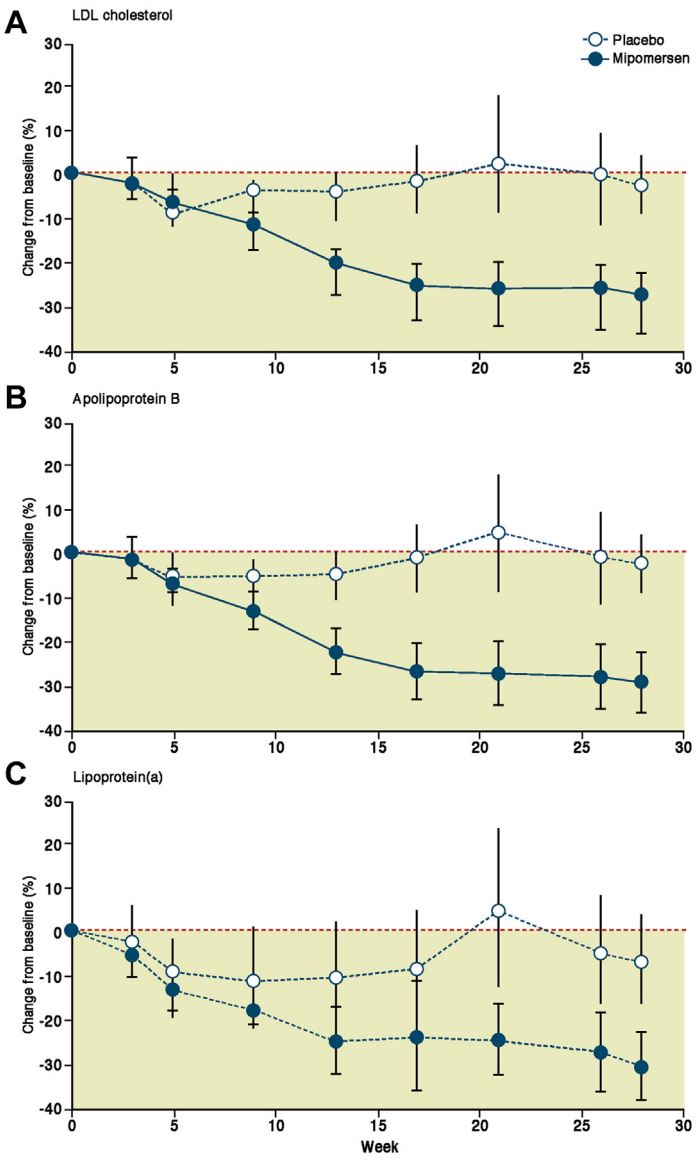

Figure 10 **Effect of Mipomersen on Low-Density Lipoprotein Cholesterol Levels**

Mean percentage change from baseline (week 0) to primary efficacy time point for low-density lipoprotein cholesterol (LDL-C) **(A)**, apolipoprotein B (APOB) **(B)**, and lipoprotein (a) (Lp(a)) **(C)** in patients with homozygous familial hypercholesterolemia (HoFH) treated with subcutaneous mipomersen, 200 mg/week, or placebo. **Error bars** indicate 95% confidence interval (CI). Reprinted with permission from Raal et al. (74).

patients (13.8%) had transaminase levels >5× normal, and 10 of 29 patients (34%) had at least 1 transaminase level >3× above normal, all of which resolved after dose reduction or discontinuation. Hepatic fat increased from 1% to 6%. No published data are available for the post-launch clinical experience.

Antisense oligonucleotide against APOB-100 mipomersen. Antisense oligonucleotides (ASO) are chemically modified nucleic acids that bind to a target mRNA, leading to its degradation, thereby reducing protein synthesis (Fig. 8). ASOs are suitable for treating diseases that are caused by or contribute to hepatic protein overproduction. APOB-100 is expressed in the liver and is essential for synthesis and integrity of VLDL and LDL, thus representing an ideal target for ASO therapy. The specific ASO mipomersen binds to APOB-100 mRNA and creates a double-stranded RNA complex that is cleaved by RNase H1, preventing formation of APOB-100. Thus, mipomersen inhibits VLDL synthesis and reduces plasma concentrations of all APOB-containing lipoproteins, including LDL. Mipomersen also effectively reduced median Lp(a) by 21% to 39% across the 4 phase III mipomersen trials, with the greatest reductions in HoFH (32%) and severe hypercholesterolemia (39%) populations (73).

Table 2 Clinical Trials With PCSK9 Inhibitors (PCSK9 Inhibitor Treated Patients Only, n = 1,551)

First Author/Trial (Ref. #)	Publication Year	Population	n	Agent	Baseline LDL-C (mg/dl)	Percentage Change From Baseline				
						LDL-C (mg/dl)	APOB (mg/dl)	Lp(a) (mg/dl)	TG (mg/dl)	HDL-C (mg/dl)
Stein et al. (80)	2012	Normal Volunteers	54	REGN727	129 to 135	−38 to −65	N/A	N/A	N/A	N/A
		HeFH	15	REGN727	134	−41 to −56	N/A	N/A	N/A	N/A
		Hypercholesterolemia	32	REGN727	111 to 179	−38 to −65	N/A	N/A	N/A	N/A
Roth et al. (81)	2012	LDL-C>100 following atorvastatin 10 mg	61	REGN727	120 to 127	−66 to −73	−54 to −58	−31 to −35	−4 to −25	3 to 6
McKenney et al. (82)	2012	LDL-C >100	152	REGN727	123 to 132	−40 to −72	−27 to −56	−8 to −29	−6 to −19	4 to 9
Stein et al. (83)	2012	HeFH	62	REGN727	140 to 170	−29 to −68	−21 to −50	−7 to −23	−5 to −17	6 to 12
MENDEL (84)	2012	LDL-C 101-189	271	AMG145	143	−37 to −53	−32 to −44	−9 to −27	−6 to −11	5 to 12
Dias et al. (85)	2012	Normal Volunteers	42	REGN727	126	−10 to −67	−16 to −57	N/A	N/A	N/A
		Hypercholesterolemia	43	REGN727	113	−24 to −75	−19 to −56	−20 to −50	N/A	N/A
RUTHERFORD (86)	2012	HeFH	111	AMG145	151 to 162	−43 to −55	−32 to −43	−19 to −27	−6 to −11	9 to 10
LAPLACE-TIMI 57 (87,91)	2012	LDL-C >85	553	AMG145	120 to 128	−42 to −66	−35 to −56	−18 to −32	−13 to −34	2 to 8
GAUSS (88)	2012	Statin Intolerance	123	AMG145	190 to 204	−41 to −63	−34 to −49	−20 to −29	−10 to −19	4 to 7
TESLA (89)	2013	HoFH	8	AMG145	441	−12 to −21	−13 to −16	−12 to −27	6 to −7	0 to 5
Fitzgerald et al. (90)	2013	Normal Volunteers	24	siRNA ALN-PCS	143	−14 to −36	N/A	N/A	N/A	N/A

To convert values for LDL-C and HDL-C to millimoles per liter, multiply by 0.02586. To convert values for triglycerides to millimoles per liter, multiply by 0.01129.
APOB = apolipoprotein B; HeFH = heterozygous familial hypercholesterolemia; HoFH = homozygous familial hypercholesterolemia; LDL-C = low-density lipoprotein-cholesterol; Lp(a) = lipoprotein (a); N/A = not available; siRNA = small interfering RNA; TG = triglycerides.

Clinical studies have been performed with a total of 775 subjects receiving 200 mg of mipomersen by weekly subcutaneous injection for 26 weeks. To date, 4 phase 3 clinical trials have been performed in HoFH patients (74), HeFH with CAD (75), severe HeFH (76) without CAD, or with high CAD risk (77), as well as a 2-year open-label extension trial in patients (n = 141) (78). LDL-C reductions ranged from 25% to 37%, with similar reductions in APOB levels. The HoFH trial, the largest randomized trial in HoFH to date, was a randomized, double blind, placebo-controlled intention-to-treat trial of 51 patients with either genetically defined HoFH or untreated LDL-C levels of >500 mg/dl plus xanthomas or evidence of HeFH in both parents. Patients were taking statin, and most were also taking other lipid-lowering drugs. In the placebo group, baseline LDL-C was 402 mg/dl and declined to 390 mg/dl at 26 weeks. In the mipomersen arm, baseline LDL-C was 440 mg/dl and was reduced to 324 mg/dl (Fig. 10). The most common side effects were injection site reactions with erythema, pain, tenderness, pruritus, and local swelling. Most side effects were mild to moderate in severity and discontinuation rate was 5% in the pooled phase 3 studies. Transaminase elevations >3× upper limit of normal occurred in 8% to 12% of patients, and all returned to normal after discontinuation of therapy. Hepatic steatosis was observed, with a median increase in liver fat of 10% compared to that of controls (76). In the open-label extension trial (78), the mean changes in LDL-C from baseline to weeks 26 (n = 130), 52 (n = 111), 76 (n = 66), and 104 (n = 53) were −28%, −27%, −27%, and −28%; and were −29%, −28%, −30%, and −31%, respectively, in APOB (78). Rates of adverse events were similar to those reported in the phase 3 trials, but median liver fat increase seen during the initial 6 to 12 months appeared to diminish with continued mipomersen exposure beyond 1 year and returned toward baseline 24 weeks after last drug dose.

Some caveats of the trials include the facts that children were included in the mipomersen but not the lomitapide trial and that the lomitapide trial included patients previously undergoing apheresis. The absolute reduction in LDL-C at 26 weeks was 170 mg/dl for lomitapide, although by 78 weeks there was some loss of efficacy for lomitapide (absolute reduction, 124 mg/dl) and 112 mg/dl for mipomersen.

Future Therapies: PCSK9 Inhibitors

PCSK9 is a protein produced by the liver and other tissues and secreted into the circulation where it binds to and leads to degradation of LDLR (7). Thus, PCSK9 acts as the terminator of the long life cycle of LDLR, which spans hundreds of recycling events. *PCSK9* gain-of-function mutations cause an FH phenotype, whereas loss-of-function mutations cause low cholesterol and protection from CVD (79). This has provided the rationale and impetus to develop inhibitors of PCSK9 to lower LDL-C. Eleven clinical trials have been published thus far with monoclonal antibodies

administered by subcutaneous injection (Table 2) (80–90). Phase 1 and 2 studies in a variety of subjects, including patients with HeFH, have shown potent reductions in LDL-C ranging from 30% to 75%. Similar reductions in APOB are observed, but triglycerides are reduced only modestly, and HDL-C levels are unchanged. Interestingly, Lp(a) levels are also reduced 10% to 50%, but the mechanisms through which this occurs have not been determined (16). Finally, a recent study in 8 patients with both true HoFH and compound HeFH demonstrated a 14% to 17% reduction (absolute reduction, −70.6 mg/dl; range, 23 to −228 mg/dl) in LDL-C (89). Interestingly, the effect was exclusive for the 6 patients with remaining LDLR function. Even though the 2 HoFH receptor-negative patients had no significant LDL-C reduction, their Lp(a) levels were reduced to the same extent (∼12% to 20% depending on dosage) as in LDLR-defective subjects, suggesting that PCSK9 may be involved in Lp(a) metabolism regardless of LDLR. Initial studies with PCSK9 inhibitors show a favorable side effect profile and no evidence of hepatic steatosis, myalgia, or transaminase elevation. Phase 3 studies are ongoing. A recent report showed that the alternative approach of inhibiting PCSK9 expression via RNA interference was also effective, causing reduction in plasma PCSK9 and LDL-C levels by 70% and 50%, respectively (90).

There are 2 phase III outcome trials in progress, including ODYSSEY (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab SAR236553 (REGN727); NCT01663402) and FOURIER (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk; NCT01764633). If approved, these drugs may revolutionize our approach to patients with severe hypercholesterolemia, including FH, with the potential to drastically reduce CVD rates in these groups of high-risk patients.

Conclusions

ADH is a disease caused by mutations in genes (*LDLR, APOB, PCSK9*) affecting the efficacy of LDL removal from the circulation. However, recent evidence suggests that many patients with a clinical FH phenotype do not carry mutations in these genes. Because it is expensive and not covered by insurance, genetic testing to diagnose ADH may lead to a paradoxical downgrading of status for many patients whose genetic cause for the elevated LDL-C is not determined. Patients with extreme hypercholesterolemia have an elevated risk of ischemic events regardless of the genotype. Our focus should be on identification and management of extreme hypercholesterolemia, with a phenotypic cascade approach to identify affected family members when appropriate. New medications approved for management of HoFH have highlighted the necessity of a new and practical way to categorize severe inherited LDL-C elevation. An approach based on plasma LDL-C levels is justifiable, inexpensive, and sensitive by definition. Novel agents in development, such as PCSK9 inhibitors, appear to be ideally suited to finally provide a method for getting most FH patients to LDL-C treatment goals.

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Key Words: familial hypercholesterolemia ■ genetics ■ LDL receptor ■ lipoproteins ■ statins.

APPENDIX

For supplemental tables, please see the online version of this article.