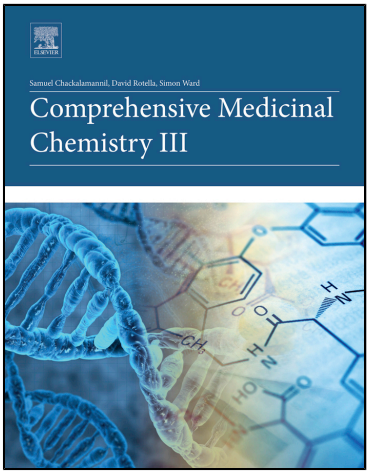

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7.18 Advances in Hypercholesterolemia

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Abbreviations

ACL Adenosine triphosphate citrate lyase
ALT Alanine aminotransferase
AMPK Adenosine monophosphate-activated protein kinase
apo(a) Apolipoprotein (a)
apoA-I Apolipoprotein A-I
apoB Apolipoprotein B
apoC-III Apolipoprotein C-III
AST Aspartate aminotransferase
CAD Coronary artery disease
CETP Cholesteryl ester transfer protein
CHD Coronary heart disease
CK Creatine kinase
CKD Chronic kidney disease
CV Cardiovascular
CVD Cardiovascular disease
CYP450 Cytochrome P450
DGAT Diacylglycerol *O*-acyltransferase
DHA Docosahexaenoic acid
EPA Eicosapentaenoic acid
ER Endoplasmic reticulum
FCS Familial chylomicronemia syndrome
FH Familial hypercholesterolemia
HDL High-density lipoprotein
HDL-C High-density lipoprotein cholesterol
HeFH Heterozygous familial hypercholesterolemia
HoFH Homozygous familial hypercholesterolemia
HR Hazard ratio
hs-CRP High-sensitivity C-reactive protein
HTG Hypertriglyceridemia
IMT Intima-media thickness
LDL Low-density lipoprotein
LDL-C Low-density lipoprotein cholesterol
LDLR Low-density lipoprotein receptor
Lp(a) Lipoprotein (a)
LPL Lipoprotein lipase
LPLD Lipoprotein lipase deficiency
mAb Monoclonal antibody
MI Myocardial infarction
MTP Microsomal triglyceride transport protein
non-HDL-C Non-high-density lipoprotein cholesterol
NPC1L1 Niemann–Pick C1-like 1
PCSK9 Proprotein convertase subtilisin/kexin type 9
Q2W Every 2 weeks
Q4W Every 4 weeks
RCT Randomized clinical trial
RLP-C Remnant-like particle cholesterol
TC Total cholesterol
TG Triglycerides
ULN Upper limit of normal
VLDL Very-low-density lipoprotein
VLDL-C Very-low-density lipoprotein cholesterol

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7.18.1 Introduction

Atherosclerosis is a chronic inflammatory disease of the arterial walls, characterized by a progressive accumulation of lipids. One of the earliest events in the formation of the atherosclerotic lesion is represented by the infiltration of low-density lipoprotein (LDL) within the artery wall. Here, LDL is oxidized by various mechanisms and subsequently greatly internalized by macrophages, which become foam cells.[1] This process, in turn, induces further deposition of lipids and activates a cascade of inflammatory processes that lead to the formation of atherosclerotic plaque. A large number of studies have recognized low-density lipoprotein cholesterol (LDL-C) level as a relevant risk factor for cardiovascular (CV) disease and established the strong and direct relationship between high LDL-C levels and coronary heart disease (CHD), suggesting that decreasing LDL-C levels significantly reduce the CV risk.

From a biological point of view, the "normal" concentrations of LDL-C are much lower than those observed in modern societies. This suggestion derives from the old observation that optimal plasma concentration of LDL-C should be about 25 mg dL^{-1}, since above this value the low-density lipoprotein receptor (LDLR) is constantly saturated.[2] This hypothesis is supported by the observation that individuals with genetically determined low levels of LDL-C are healthy and exhibit very low incidence of CV events.[3,4]

Several clinical trials have shown that reducing LDL-C decreases the incidence of CV events. A meta-analysis of data from trials of statins showed in fact that, during a mean of 5 years, a 12% reduction in all-cause mortality per mmol L^{-1} reduction in LDL-C, a 19% reduction in coronary mortality, and a 17% reduction in any vascular cause of mortality were observed.[5] These effects were independent of the initial lipid profile or other presenting characteristics, and the proportional reductions were similar in all subgroups of patients examined.[5] In addition, the comparison between more intensive and less intensive statin therapy showed that additional reduction in LDL-C levels achieved with more intensive therapy further reduces the incidence of major vascular events (-13% coronary death or nonfatal myocardial infarction (MI), -19% coronary revascularization, and -16% ischemic stroke).[6] These meta-analyses suggest that the higher the degree of reduction of LDL-C levels, the greater the benefit in terms of reduction of CV risk. This means that patients at high CV risk may benefit from achieving the largest LDL-C reduction. Current therapeutic guidelines suggest that in patients at very high CV risk (such as patients with established cardiovascular disease (CVD), diabetes, moderate to severe coronary kidney disease, and familial hypercholesterolemia (FH)), optimal LDL-C is <70 mg dL^{-1} (<1.8 mmol L^{-1}), in those at high CV risk <100 mg dL^{-1} (<2.6 mmol L^{-1}) and in subjects at moderate risk <115 mg dL^{-1} (<3.0 mmol L^{-1}).[7,8] Moreover, the therapeutic goals of LDL-C should be not only achieved but also maintained over time to obtain the clinical benefit; treatments need to be modulated based on the overall CV risk of the individual patient and according to the objectives to be achieved. This means the choice of the drug with the right effectiveness, a dose selection according to the objectives, and eventually the use of additional drugs with complementary mechanisms of action to increase the efficacy of the therapy.

Despite the evidence confirming the beneficial effect of a significant LDL-C level reduction in patients at very high CV risk, many of these patients often do not reach their LDL-C goal with the starting therapy. When a reduction higher than 50% is required, it is necessary to use a high dose of high-potency statins (atorvastatin and rosuvastatin) (**Fig. 1**) or, alternatively, combined lipid-lowering therapies. The choice of the most appropriate therapeutic approach can be done taking into account either the LDL-C target or distance of LDL-C from the target. The achievement of the therapeutic target implies the choice of pharmacological strategies specific to each subject, according to the goal to be achieved; thus, a high distance from the target requires the administration of a high-potency statin or, alternatively, a combination of cholesterol-lowering drugs with different mechanisms of action.

Familial hypercholesterolemia. Among patients with high CV risk, those with FH present a high risk of premature CHD, due to lifelong exposure to high plasma LDL-C levels.[8] FH is caused by mutations in genes encoding proteins involved in the metabolism of LDL, such as LDLR, apolipoprotein B (apoB), proprotein convertase subtilisin/kexin type 9 (PCSK9), and LDLR adaptor protein; mutations in LDLR gene account for the vast majority of FH cases.[8]

Heterozygous familial hypercholesterolemia (HeFH) patients present a residual LDLR activity (up to 50%) and are characterized by two- to threefold elevation in plasma cholesterol levels and development of early coronary atherosclerosis (usually before 50 years); homozygous familial hypercholesterolemia (HoFH) patients may be receptor-defective, with a significantly reduced LDLR pathway (2–10% activity), or receptor-negative, characterized by an LDLR activity $<2\%$. The HoFH presents more severe CV conditions compared with subjects with receptor deficiency.[9] The lack of LDLR in receptor-negative HoFH determines the exposure to very high cholesterol levels (>500 mg dL^{-1} and >12.8 mmol L^{-1}) from childhood, the occurrence of cutaneous xanthomas prior to 4 years of age, childhood CHD, and even death from MI prior to 20 years of age if untreated.[9,10] Lifestyle interventions (low saturated fat, low cholesterol diet, physical activity, and not smoking) are strongly encouraged, but aggressive and adequate lipid-lowering treatments are crucial to lower LDL-C levels drastically. Despite the fact that statins are the first-choice drug for the treatment of hypercholesterolemia,[8,11] their efficacy is strictly related to the presence of a functional LDLR and thus may be effective in HeFH or in receptor-defective HoFH.[8,9] In LDLR-negative HoFH patients, statins, although inducing a modest reduction of LDL-C ($\sim 20\%$, probably due to alternative mechanism of action independent of LDLR), do not allow the achievement of the recommended LDL-C level target.[12] In addition, some subjects may exhibit intolerance to statins, leading to therapy discontinuation. All these observations suggest the need of new therapeutic options to decrease LDL-C levels in these very high-risk patients, by using combined lipid-lowering therapies (often in addition to apheresis treatment), with drugs having different mechanisms of action as described in the succeeding text, possibly independent of LDLR that may guarantee a higher reduction of LDL-C levels.

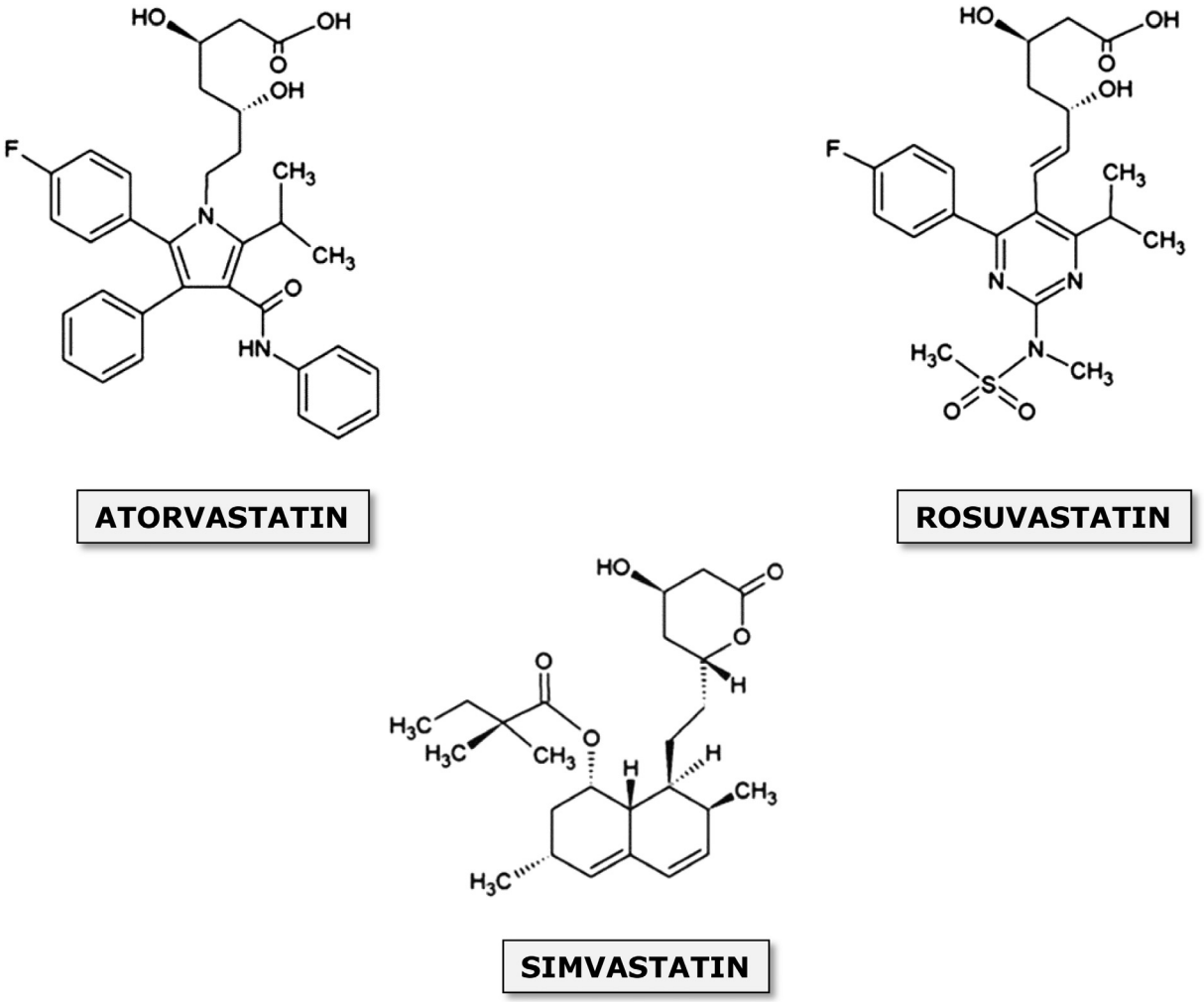

Fig. 1 Structure of atorvastatin, rosuvastatin, and simvastatin.

7.18.2 Statins in the Prevention of CV Disease

Several clinical trials have established the efficacy of statins in reducing CV morbidity and mortality in both primary and secondary prevention.[6,13–18] Statins reduce LDL-C levels by inhibiting 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, thus inhibiting the endogenous synthesis of cholesterol. This, in turn, results in the upregulation of LDLR and in the subsequent reduction of circulating LDL particles. A meta-analysis of 14 randomized clinical trials with 90,056 participants showed an overall safety and benefit of statin therapy [5]: during a mean of 5 years, there was a 12% proportional reduction in all-cause mortality per mmol L^{-1} reduction in LDL-C, with significant reduction in coronary mortality (-19%, $P<0.0001$), MI or coronary death (-23%, $P<0.0001$), and fatal or nonfatal stroke (-17%, $P<0.0001$).[5] An overall $\sim$20% reduction in the incidence of CV events per mmol L^{-1} LDL reduction was reported.[5] When trials of more intensive versus less intensive statin therapy were analyzed, more intensive regimens produced an additional 15% ($P<0.0001$) reduction in major vascular events,[6] suggesting that further reducing LDL-C levels safely translates into a further clinical benefit.

However, despite the significant reduction of CV events in statin-treated patients, certain patients continue to experience CV events, referred to as "residual risk," even in the presence of well-controlled LDL-C levels.[19] The evidence suggests that atherogenic dyslipidemia, that is, alterations in other lipids (such as high triglycerides (TG) and low high-density lipoprotein cholesterol (HDL-C)), may account for this effect.[20] In addition, an increasing number of subjects are treated with statins, often in combination with other drugs, thus increasing the probability of drug–drug interactions and the occurrence of adverse side effects.[21] Finally, the adherence to statin therapy is not always optimal, as many patients discontinue statin therapy due to adverse events.

The most common adverse events reported with statin are skeletal muscle-related disorders (generally referred to as myopathy). Despite randomized clinical trials reported a 1.5–5% incidence of statin-induced myopathy,[22,23] in clinical practice the frequency appears to be higher.[24] This difference can be partly attributed to the patient inclusion criteria adopted in the clinical trials, which tend to exclude subjects with comorbidities, older subjects, or patients with a history of muscle disorders.[24,25] In addition, increased

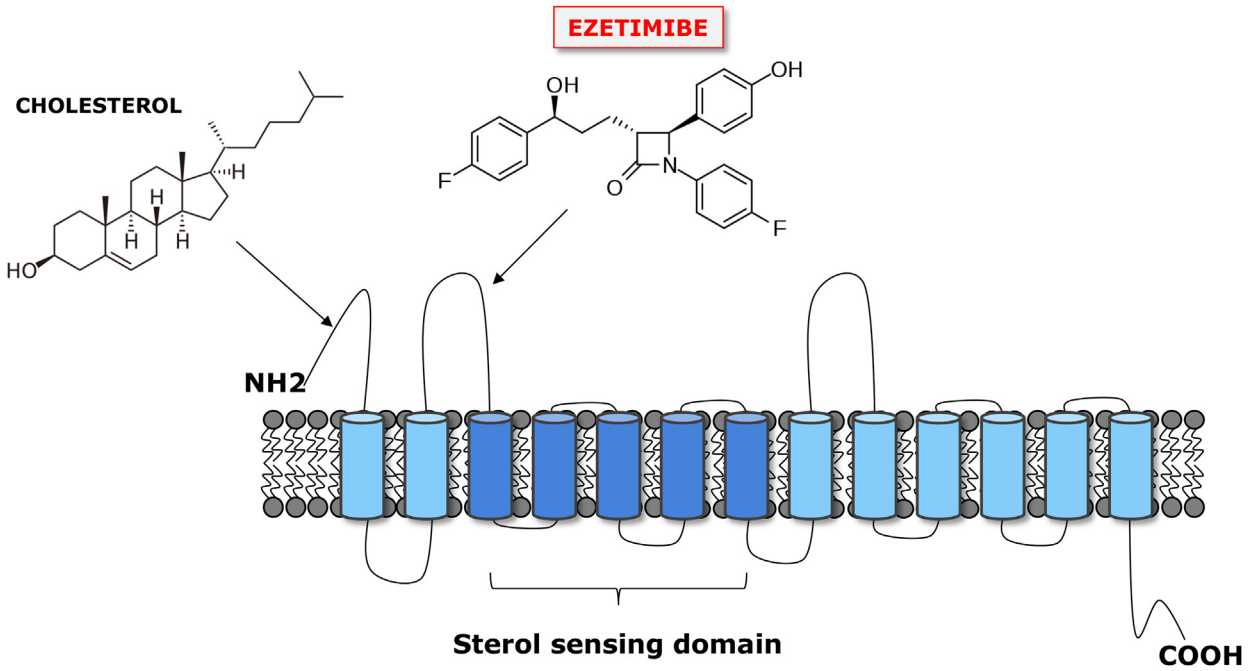

Fig. 2 Structure of human NPC1L1. NPC1L1 contains 13 transmembrane domains, including sterol-sensing domain formed by membrane-spanning helices with short intervening loops. The extracellular N-terminal domain of NPC1L1 directly binds cholesterol; ezetimibe binds to the loop C.

levels of creatine kinase (CK) are used as a marker for statin-induced myopathy, but myopathy occurrence not always associates with these alterations. Finally, less significant signs of myopathy (including fatigability or weakness) are often not considered as relevant.[25] Altogether, these observations may account for the underestimation of muscle-related side effects in statin-treated patients in the clinical trials.

Statin-related myopathy occurs particularly with high-dosage statin regimens, and thus, its incidence is higher in high CV risk patients who need more aggressive lipid-lowering therapies or in patients with comorbidities, due to metabolic interactions with other drugs.[26,27] They include less severe manifestations (asymptomatic moderate serum CK elevation or muscle pain in the absence of CK elevation)[28] up to the most severe and rare rhabdomyolysis.[28,29] Several risk factors may increase the probability of myotoxicity related to statin therapy: chemicophysical properties of statins (lipophilic statins seem to induce myotoxicity more than hydrophilic statins), administration of concomitant drugs that can interact with statins, and patient-related risk factors (age, female gender, and genetic factors).[29] Discontinuation of statin therapy is common among patients experiencing muscle-related adverse effects, but several pharmacological approaches may be adopted to treat patients intolerant to statins. First, a statin rechallenge may be tolerated by patients; the rechallenge may be done by reintroducing the same statin at a lower dose or by introducing a different statin (such as a more potent statin at a low dose) or by using the noneveryday statin administration (this is possible with potent statins with longer half-life, such as rosuvastatin and atorvastatin).[29] Alternatively, the lowest dose of statin tolerated may be combined with nonstatin lipid-lowering drugs.[29] Several nonstatin drugs have been approved for the treatment of dyslipidemia, but, despite an improvement of the lipid profile, results from clinical trials could not support their use as monotherapy or in combination with statins, with the exception of ezetimibe (Fig. 2).[30,31] In fact, the addition of niacin to statin therapy did not show any further clinical benefit, compared with statin therapy [32,33]; similarly, clinical trials on fenofibrate showed a benefit only in particular subgroups of patients (i.e., those with high TG and low HDL-C levels).[34,35] In addition, the difficult-to-manage high CV risk patients such as those with FH raised the need of new lipid-lowering drugs that could add significant clinical benefit beyond statin treatment.

7.18.3 Novel Therapeutic Approaches in the Management of Dyslipidemia

In recent years, several therapeutic approaches have been investigated for reducing plasma cholesterol and/or TG levels through different mechanisms of action. Specific therapies were explored not only for the treatment of monogenic homozygous forms of dyslipidemia including familial hypercholesterolemia or chylomicronemia syndrome but also for statin-intolerant patients.

7.18.3.1 Targeting Plasma Cholesterol Levels

7.18.3.1.1 Ezetimibe

Niemann–Pick C1-like 1 (NPC1L1) protein plays a central role in the intestinal absorption of cholesterol and the regulation of cholesterol plasma levels.[36,37] Its expression and localization are strictly regulated by the cellular content of cholesterol: when cells

are enriched in cholesterol, NPC1L1 is localized in the endocytic recycling compartment, but in cells depleted of cholesterol, NPC1L1 translocates to the cell surface to bind extracellular cholesterol[38,39] (Fig. 2). In humans, NPC1L1 is expressed also in the liver, where it prevents excessive loss of biliary cholesterol.[40]

The evidence of the involvement of NPC1L1 in the process of cholesterol absorption derives from observations in animal studies. NPC1L1-deficient mice have a significantly reduced cholesterol absorption (−69%) compared with wild-type mice.[41] In apoE knockout mice, the deficiency of NPC1L1 largely decreased cholesterol absorption, protected them from diet-induced hypercholesterolemia, and prevented atherosclerotic lesion formation.[42,43] On the other hand, NPC1L1 overexpression in cultured cells increased cholesterol uptake in cells,[44] and cholesterol feeding of NPC1L1$^{-/-}$/LDLR$^{-/-}$ knockout mice transgenically expressing human NPC1L1 resulted in significantly increased cholesterol absorption and cholesterol levels compared with the double knockout mice.[45] In humans, carriers of NPC1L1 inactivating mutations exhibit lower LDL-C levels compared with noncarriers and exhibited a relative reduction of 53% in the risk of CHD.[46] These observations suggest that pharmacological inhibition of NPC1L1 can be a therapeutic approach for the treatment of hypercholesterolemia in humans.

Ezetimibe is a selective inhibitor of cholesterol absorption that reduces the cholesterol uptake in enterocytes by inhibiting NPC1L1[47] (Fig. 2). Ezetimibe is rapidly absorbed from the gastrointestinal tract and transformed into its glucuronides. The phenolic glucuronide is the main metabolite detectable in human plasma and accounts for about 90% of the total ezetimibe; it localizes more avidly in the intestine compared with ezetimibe and has similar or even higher cholesterol-lowering activity compared with the parent compound.[48,49]

Statins and ezetimibe have different and complementary mechanisms of action, and thus, the combination statin + ezetimibe may represent a successful approach for the prevention of CV disease and allow the treatment of subjects that manifest intolerance to high-dose statins. In addition, the statin-induced inhibition of cholesterol synthesis results in an increase of absorption markers, and, on the contrary, the reduced cholesterol absorption induced by ezetimibe results in the increase of cholesterol synthesis [50]; this would reduce the efficiency of the single drugs, while the combination decreases both cholesterol synthesis and absorption.[50]

Several clinical trials have shown that adding ezetimibe to statin therapy determines an additional 20% reduction of LDL-C levels[51–54] (Table 1). A pooled analysis of over 21,000 subjects from 27 clinical trials showed that combining ezetimibe with a statin induces a greater lipid-lowering effect than statin monotherapy.[55] Similarly, LDL-C lowering was significantly higher in patients with CHD or CHD equivalent treated with ezetimibe added to current statin therapy compared with patients who titrated the statin doses.[56]

Also, diabetic patients seem to benefit from the combination ezetimibe + statin: the *RESEARCH* (*Recognized Effect of Statin and Ezetimibe Therapy for Achieving LDL-C Goal*) trial reported that the ezetimibe + statin induced a higher LDL-C reduction compared with doubling the statin dose (−24.6% vs. −10.9%, $P<0.0001$)[57]; in addition, more subjects reached their LDL-C goals in the group treated with ezetimibe + statin versus the group treated with a doubled statin dose (89.3% vs. 51%, $P<0.0001$).[57] The combination therapy also improved the atherogenic lipid profile characteristic of diabetes more effectively than statin therapy; this effect can be attributed to a higher reduction of small dense LDL (−20.5% vs. −3.7%) and remnant-like particle cholesterol (RLP-C) (−19.7% vs. +5.5%).[57] Diabetic patients seem to benefit from the combination therapy ezetimibe + statin more than nondiabetic subjects, as they achieve significantly higher reductions in LDL-C and non-high-density lipoprotein cholesterol (non-HDL-C); it has been hypothesized that diabetic patients might have a higher expression of NPC1L1, but a defined explanation is still lacking.[58]

Contrasting results have been reported on the ability of ezetimibe to reduce the carotid intima-media thickness (IMT), a marker of subclinical atherosclerosis. In the *ENHANCE* (*Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression*, NCT00552097) trial, which compared the effect of ezetimibe + simvastatin (10 + 80 mg) or simvastatin (Fig. 1) alone on the progression of atherosclerosis in HeFH patients, changes in the carotid IMT did not differ in the groups, despite lower LDL-C levels observed in patients treated with the combination therapy (−55.6% vs. −39.1% with statin monotherapy, $P<0.01$)[59] (Table 1). The *ARBITER 6-HALTS* (Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 6-HDL and LDL Treatment Strategies in Atherosclerosis, NCT00397657) trial, performed in patients with CHD or CHD equivalent to evaluate the effect of ezetimibe or extended-release niacin added to a chronic statin therapy, reported a lack of effect of ezetimibe that instead resulted in carotid IMT progression[60] (Table 1). Lack of effect of ezetimibe added to statin therapy on IMT has been reported also in other studies.[61,62] On the contrary, the *SANDS* (*Stop Atherosclerosis in Native Diabetics Study*, NCT00047424) trial showed that, compared with standard lipid-lowering therapies, aggressive lipid-lowering treatments induced a regression of carotid IMT in type 2 diabetic patients[63] (Table 1). Among subjects treated with aggressive lipid-lowering treatments, those receiving ezetimibe exhibited a greater reduction despite similar LDL-C reductions[64] (Table 1). One possible explanation for these discrepancies is the baseline carotid status: if the patients have IMT values within the normal range, the chance that a cholesterol-lowering therapy may be effective on this parameter is lower than in subjects with significant IMT values.

Two studies have reported a beneficial effect of ezetimibe + statin on coronary atherosclerosis: besides a greater reduction in the plaque volume,[65] a higher increase of the fibrous cap thickness was observed, suggesting a possible role for ezetimibe in the stabilization of atherosclerotic plaque[66] (Table 1).

Ezetimibe in the prevention of cardiovascular disease. Several studies have established the LDL-C-lowering ability of ezetimibe, showing a further reduction of 23% when added to a statin therapy [55,67]; however, few clinical trials have evaluated the clinical benefit of the addition of ezetimibe to statin therapy. The *SHARP* (Study of Heart and Renal Protection, NCT00125593) trial, performed in patients with moderate to severe kidney disease, evaluated the effect of ezetimibe + simvastatin or placebo

Table 1 Effects of ezetimibe combined with a statin versus statin monotherapies on LDL-C levels and clinical outcomes

Clinical trials	*Subjects*	*Duration*	*LDL-C (percent change from baseline)*	*Clinical outcomes*	*P*
RESEARCH[57]	T2DM	12 weeks	Eze + Stat: −24.6% DST: 1–10.9%		
ENHANCE,[59] NCT00552097	FH	24 months	Eze + Simva: −55.6% Simva: −39.1%	Carotid IMT (change from baseline, mm) Eze + Simva: +0.0111 + 0.0038 Simva: +0.0058 + 0.0037	NS
ARBITER 6-HALTS,[60] NCT00397657	CHD or CHD equivalent on stable statin therapy	14 months	Eze: −22.5% Niacin: −12.6%	Carotid IMT (change from baseline, mm) Eze: −0.0007 ± 0.0035 Niacin: −0.0142 ± 0.0041	NS $P = 0.001$
SANDS,[63,64] NCT00047424	T2DM	36 months	Aggressive LLT: −31% Standard LLT: +1% Aggressive Eze + Stat: −31.1% Aggressive statin alone: −32.3%	Mean change CIMT (mm) Aggressive LLT: −0.017 ± 0.12 Standard LLT: +0.041 + 0.14 Aggressive Eze + Stat: −0.025 (−0.05 to 0.003) Aggressive statin alone: −0.012 (−0.03 to 0.008)	$P < 0.0001$ $P < 0.0001$
Masuda et al.[65]	Stable CAD	6 months	Eze + Rosuva: −55.8% Rosuva: −36.8%	% Change in plaque volume Eze + Rosuva: −13.2% Rosuva: −3.1%	$P = 0.05$
Habara et al.[66]	Angina pectoris	9 months	Eze + Fluva: −34.0% Fluva: −8.3%	Change in the fibrous cap thickness (mm) Eze + Fluva: +0.08 + 0.08 Fluva: +0.04 ± 0.06	$P < 0.001$
SHARP,[68] NCT00125593	CKD	4.9 years	Eze + Simva: −68% Placebo: −14%	Major atherosclerotic events Eze + Simva: 11.3% Placebo: 13.4%	$P = 0.0021$
IMPROVE-IT,[31] NCT00202878	ACS	6 years	Eze + Simva: −42.8% Simva: −25.9%	Death from cardiovascular causes, major coronary event, or nonfatal stroke Eze + Simva: 32.7% Simva: 34.7%	$P = 0.016$

FH, familial hypercholesterolemia; *CHD*, coronary heart disease; *T2DM*, type 2 diabetes mellitus; *CAD*, coronary artery disease; *CKD*, chronic kidney disease; *ACS*, acute coronary syndrome; *Eze*, ezetimibe; *Stat*, statin; *Simva*, simvastatin; *Fluva*, fluvastatin; *Rosuva*, rosuvastatin; *LLT*, lipid-lowering therapy.

administration for 4.9 years [68]; the combination therapy reduced LDL-C levels by 33 mg dL^{-1} (0.84 mmol L^{-1}) and decreased the incidence of major atherosclerotic events (including nonfatal MI, coronary death, nonhemorrhagic stroke, and arterial revascularization) by 17%[68] (**Table 1**). When considering chronic kidney disease (CKD) patients with LDL-C not at target despite statin therapy (>120 mg dL^{-1} and >3.1 mmol L^{-1}), the combination therapy was more safe than doubling the dose of statins, as the incidence of adverse events was significantly lower.[69] These observations suggest that ezetimibe is a helpful and safe add-on to statin therapy to treat high CV risk patients such as those with CKD.

The *IMPROVE-IT* (*Improved Reduction of Outcomes: Vytorin Efficacy International Trial*, NCT00202878) compared the effect of a 6-year administration of ezetimibe + simvastatin (10/40 mg) or simvastatin (40 mg) alone in patients with a recent acute coronary syndrome and LDL-C levels at target.[31] At the end of the study, the LDL-C level was significantly lower in the group treated with ezetimibe + simvastatin compared with those treated with simvastatin alone (53.7 mg dL^{-1} vs. 69.5 mg dL^{-1}, $P < 0.001$) (**Table 1**); furthermore, more patients treated with the combination therapy reached LDL-C levels <70 mg dL^{-1} (<1.8 mmol L^{-1}).[31] This effect on LDL-C level translated into a higher reduction of the primary end point (a composite of CV death, nonfatal MI, unstable angina requiring hospitalization, coronary revascularization, and nonfatal stroke) in the group treated with ezetimibe + simvastatin group (32.7% vs. 34.7% with simvastatin alone, $P = 0.016$)[31] (**Table 1**). Secondary analyses of this study have shown the clinical benefit of adding ezetimibe to statin in subgroups of patients; as an example, women receiving the combination therapy exhibited a 12% reduction of the relative risk of the primary end point, compared with a 5% reduction in men [70]; older patients (≥75 years) showed a greater benefit from the combination therapy compared with younger patients (<65 years HR 0.98, ≥65 years HR 0.89, and ≥75 years HR 0.80). Moreover, type 2 diabetic patients seem to benefit more than nondiabetics from the combination therapy (14% reduction of the relative CV risk vs. 2% in nondiabetics).[71] Combined therapy was also superior to simvastatin alone in reducing the incidence of nonhemorrhagic stroke (HR 0.78, $P = 0.008$).[72] All these analyses showed that adverse events did not differ among the various subgroups.[72]

Ezetimibe in the treatment of FH. In FH patients treated with the combination ezetimibe + statin, the levels of total cholesterol (TC) and LDL-C were lower than in those treated with statin alone.[59,73,74] However, no difference was observed in the reduction of carotid IMT [59]; this is likely due to the fact that the vast majority of FH patients enrolled in that study were on statin therapy long before entering the trial, resulting in the attenuation of IMT progression, and thus, a further LDL-C reduction was not able to further reduce the carotid IMT. Other studies with statin-naive patients have shown a regression.[75] Despite these considerations, contrasting results have been reported on the effect of the combination ezetimibe + simvastatin, which, in other studies, was reported to decrease significantly the carotid IMT in two groups of HeFH patients, one with a history of acute MI and the other with carotid lesions but no history of CV events.[76]

7.18.3.1.2 PCSK9 inhibitors

PCSK9 is a proteinase that inhibits the recycling of LDLRs by causing their lysosomal degradation, mainly synthesized and secreted by the liver. PCSK9 activity results in reduced expression of hepatic LDLR and increased circulating LDL-C levels (Fig. 3). In addition, statins increase PCSK9 expression,[77] which would translate in a reduced efficacy of statin therapy. Thus, inhibiting PCSK9 expression/activity represents a therapeutic approach that can result in the reduction of LDL-C levels. PCSK9 inhibition is obtained by the means of specific monoclonal antibodies (mAbs). Several clinical studies have shown that anti-PCSK9 monoclonal antibody monotherapies significantly decreased TC and LDL-C, with an overall incidence of adverse effects similar between the treatment and placebo groups.[78] Moreover, since statins induce PCSK9 expression, the addition of a PCSK9 mAb to a statin may result in an increased therapeutic effect.[79,80]

Evolocumab, alirocumab and bococizumab are human mAbs against PCSK9 leading to increased hepatic LDLR expression and LDL clearance. Two recent meta-analyses have evaluated the efficacy and safety of PCSK9 antibodies in randomized controlled clinical trials.[81,82] Li et al.[82] analyzed 20 RCTs including 6464 hypercholesterolemic patients and 3416 controls; participants of 16 studies were hypercholesterolemic and included also HeFH patients; three studies were performed only in HeFH and one in HoFH.[82] Most of these trials had a duration of 8–24 weeks. In some studies (10), the PCSK9 mAb was administered as a monotherapy; in the others, the antibodies were administered in addition to other lipid-lowering therapies. The analysis of these trials showed that treatment with PCSK9 mAbs significantly reduces LDL-C levels, with a weighted mean change

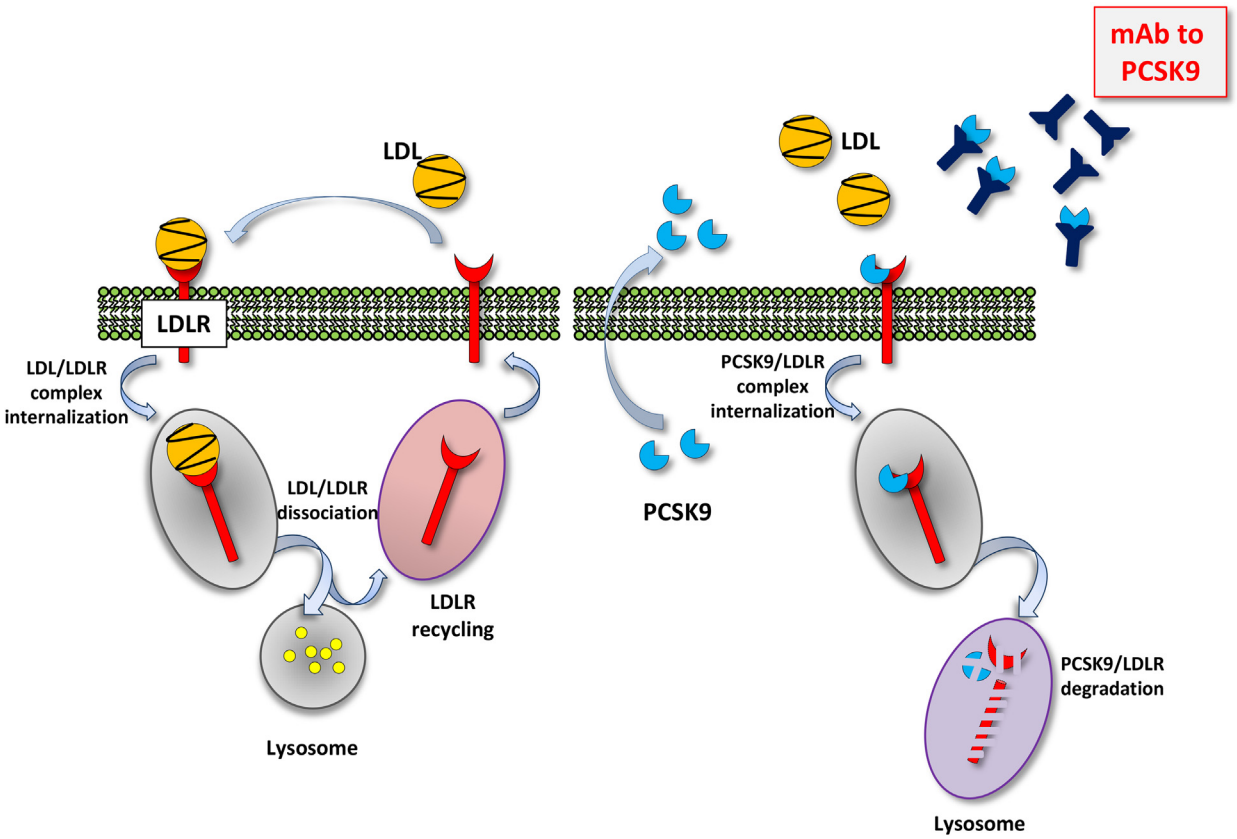

Fig. 3 Mode of action of PCSK9 inhibitors. In the absence of PCSK9, LDL binds to LDLR. After internalization, the LDL-LDLR complex dissociates, LDL undergoes lysosomal degradation, and LDLR is recycled to the cell surface. In the presence of PCSK9, LDLR is degraded within the cells, leading to increased levels of circulating LDL-C. Monoclonal antibodies neutralize secreted PCSK9, rendering it unable to bind to the LDLR. *LDL-C*, LDL cholesterol; *LDLR*, LDL receptor; *PCSK9*, proprotein convertase subtilisin/kexin type 9.

of -65.29 mg dL^{-1}; also, other lipids and apoproteins significantly changed (TC, -60.04 mg dL^{-1}; TG, -12.21 mg dL^{-1}; apoB, -41.01 mg dL^{-1}; HDL-C, $+3.40$ mg dL^{-1}; and apolipoprotein A-I (apoA-I), $+6.75$ mg dL^{-1}); lipoprotein (a) (Lp(a)) was significantly reduced following treatment with PCSK9 mAbs (standardized mean difference: -0.94).[82] Despite the reduction of LDL-C levels was greater in patients treated with anti-PCSK9 monotherapy than in those who had received combined therapy (-69.84 mg dL^{-1} vs. -60.16 mg dL^{-1}), the difference was not significant. Patients with HeFH showed a higher LDL-C level reduction compared with patients with non-FH (-79.02 mg dL^{-1} vs. -62.38 mg dL^{-1}). Interestingly, trials with a duration $\leq$12 weeks obtained greater reductions of LDL-C levels compared with longer trials (-70.89 mg dL^{-1} vs. -55.0 mg dL^{-1}). Mild-to-moderate adverse events as well as serious adverse events did not differ between patients receiving PCSK9 and patients receiving placebo or statin monotherapy. Navarese et al. analyzed 24 RCTs (8 phase 2 and 16 phase 3 trials) including 10,159 patients (6187 receiving anti-PCSK9 and 3972 controls).[81] LDL-C levels were reduced by almost 50% in patients treated with PCSK9 mAb; the reduction was greater when compared with placebo than when compared with ezetimibe (-58.77% vs. -36.17%, $P<0.001$). Also TC and Lp(a) levels were significantly reduced following the treatment with anti-PCSK9 (-31% and -25%, respectively), while HDL-C levels were increased by 6.30% ($P<0.001$). All-cause mortality was significantly reduced in the group of patients receiving anti-PCSK9 (mortality rates: 0.31% vs. 0.53%, $P=0.015$), whereas a nonsignificant reduction of CV mortality was observed (CV mortality rates: 0.19% vs. 0.33%, $P=0.084$) [81]; the rates of unstable angina were similar in the two groups (0.04% vs. 0.08%, $P=0.34$). Treatment with PCSK9 mAb significantly reduced the percentage of patients experiencing an increase in the levels of CK (1.96% vs. 2.31%, $P=0.026$).[81] The overall incidence of serious adverse effects was similar in patients treated with anti-PCSK9 and in patients not receiving the antibodies (9.26% vs. 7.73%, $P=0.879$).[81] Thus, from these two meta-analyses, it appears that anti-PCSK9 antibody treatment effectively corrects lipid abnormalities and reduces the CV mortality in hypercholesterolemic patients.

Evolocumab. A large number of clinical trials have assessed the efficacy and safety of evolocumab in different groups of patients. Most of these studies were 12-week phase 2 and phase 3 trials that reported significant reductions of LDL-C levels compared with either placebo or ezetimibe.[83,84] Tested as monotherapy in *MENDEL* (*Monoclonal Antibody against PCSK9 to Reduce Elevated LDL-C in Subjects Currently Not Receiving Drug Therapy for Easing Lipid Levels*, NCT01375777) and *MENDEL-2* (NCT01763827) trials, the administration of evolocumab for 12 weeks significantly reduced LDL-C levels; similar reductions were observed with 140 mg every 2 weeks (Q2W) or 420 mg every 4 weeks (Q4W) (-50.9% and -48.0% from baseline in MENDEL and -57.0% and -56.1% from baseline in MENDEL-2)[85,86] (**Table 2**). Comparable reductions were reported by other phase 2 trials in different groups of hypercholesterolemic patients.[84]

In *LAPLACE-TIMI 57* (*Low-Density Lipoprotein Cholesterol Assessment with PCSK9 Monoclonal Antibody Inhibition Combined with Statin Therapy*, NCT01380730), hypercholesterolemic patients with LDL-C >85 mg dL^{-1} (>2.2 mmol L^{-1}) despite lipid-lowering therapy (statin with or without ezetimibe), the administration of evolocumab at different doses (70, 105, or 140 mg Q2W or 280, 350, or 420 mg Q4W) for 12 weeks produced a dose-dependent LDL-C reduction[87] (**Table 2**); reductions were comparable in all patient subgroups. Of note, 94% of patients taking evolocumab 140 mg Q2W achieved an LDL-C level <70 mg dL^{-1} (<1.8 mmol L^{-1}), with a mean LDL-C value of 43 mg dL^{-1} (1.1 mmol L^{-1}).[87] In phase 3 *LAPLACE-2* (NCT01763866), patients taking moderate-intensity (atorvastatin 10 mg, simvastatin 40 mg, or rosuvastatin 5 mg) or high-intensity (atorvastatin 80 mg or rosuvastatin 40 mg) therapy were administered with evolocumab (140 mg Q2W or 420 mg Q4W) or placebo or ezetimibe (only in atorvastatin-taking patients).[88] At the mean of weeks 10 and 12, percent reductions were similar across the statin groups and the two evolocumab administration regimens (66–75% with Q2W dosing and 63–75% for Q4W dosing vs. placebo)[88] (**Table 2**). In patients treated with atorvastatin, the addition of evolocumab was significantly more efficacious in reducing LDL-C levels compared with ezetimibe, and greater proportions of patients reached the LDL-C target <70 mg dL^{-1} (<1.8 mmol L^{-1}) with evolocumab than with ezetimibe.[88] When added to a background lipid-lowering therapy for 52 weeks in hypercholesterolemic patients in the *DESCARTES* (*Durable Effect of PCSK9 Antibody Compared with Placebo Study*, NCT01516879) trial, evolocumab significantly reduced LDL-C levels (-57%) either in addition to diet alone or with low-dose (10 mg) or high-dose (80 mg) atorvastatin with or without ezetimibe, and the treatment was well tolerated[89] (**Table 2**). The ongoing *GLAGOV* (*Global Assessment of Plaque Regression with a PCSK9 Antibody as Measured by Intravascular Ultrasound*, NCT01813422) trial will establish whether LDL-C lowering with evolocumab will reduce the percent atheroma volume compared with placebo in subjects with CAD receiving lipid-lowering therapy; the treatment will end after 78 weeks and the trial has an estimated primary completion date in July 2016.

Evolocumab was evaluated in a population of hypercholesterolemic statin-intolerant patients in the phase 2 *GAUSS* (*Goal Achievement after Utilizing an Anti-PCSK9 Antibody in Statin Intolerant Subjects*, NCT01375764) study.[90] Evolocumab was given alone (280, 350, and 420 mg Q4W) or in combination with ezetimibe (420/10 mg) and compared with ezetimibe (10 mg) alone; after 12 weeks, patients who received evolocumab had a dose-dependent reduction of LDL-C levels (-40.8 to -50.7% from baseline), and the association with ezetimibe resulted in a higher decrease compared with ezetimibe alone (-63% vs. -14.8%) (**Table 2**); the maximal reduction was obtained within 2 weeks after starting the treatment.[90] In the group of evolocumab alone, a higher proportion of patients reached the LDL-C targets <100 mg dL$-^{1}$ (<2.6 mmol L^{-1}) or <70 mg dL^{-1} (<1.8 mmol L^{-1}) (54% and 18%) compared with ezetimibe alone (7% and 0%); the combination evolocumab + ezetimibe greatly increased the proportion of patients at target (90% and 62%, respectively).[90] Also TC, non-HDL-C, apoB, and Lp(a) were significantly reduced following evolocumab administration either alone or in combination with ezetimibe; HDL-C and apoA-I increased, although statistically significant differences were observed only with high-dose evolocumab.[90] Overall, the administration of evolocumab was well tolerated, with similar percentages of patients reporting adverse effects in the group of evolocumab and in the group of ezetimibe; myalgia was the most common side effect occurring in 7.4% taking evolocumab alone, in 20% taking evolocumab + ezetimibe, and

Table 2 Results from clinical trials on evolocumab

Clinical trial (ClinicalTrials.gov identification number)	*Subjects*	*Duration*	*Background LLT*	*Intervention*	*LDL-C (percent change from baseline)*	*Primary end point for ongoing trials*
MENDEL, NCT01375777[85]	LDL-C $\geq$100 and $<$190 mg dL^{-1}; TG $<$400 mg dL^{-1}	12 weeks	None	70, 105, or 140 mg Q2W 280, 350, or 420 mg Q4W	Q2W: $-$26.7% to $-$36.7% versus Eze $-$37.3% to $-$47.2% versus placebo Q4W: $-$25.2% to $-$34.1% versus Eze $-$43.6% to $-$52.5% versus placebo	
MENDEL-2, NCT01763827[86]	LDL-C $\geq$100 and $<$190 mg dL^{-1}; TG $<$400 mg dL^{-1}	12 weeks	None	140 mg Q2W 420 mg Q4W	Q2W: $-$39.3% versus Eze; $-$57.4% versus placebo Q4W: $-$37.6% versus Eze; $-$54.8% versus placebo	
LAPLACE-TIMI 57, NCT01380730[87]	Fasting LDI-C $\geq$85 mg dL^{-1}	12 weeks	Statin $\pm$ ezetimibe	70, 105, or 140 mg Q2W 280, 350, or 420 mg Q4W	Q2W: $-$41.8% to $-$66.1% versus placebo Q4W: $-$41.8% to $-$50.3% versus placebo	
LAPLACE-2, NCT01763866[88]	Fasting LDL-C $\geq$150 mg dL^{-1} if not on statin Fasting LDL-C $\geq$100 mg dL^{-1} if not on intensive statin Fasting LDL-C $\geq$80 mg dL^{-1} if on intensive statin	12 weeks	Atorva 10 $\pm$ Eze 10 Atorva 80 $\pm$ Eze 10 Rosuva 5 Rosuva 40 Simva 40	140 mg Q2W 420 mg Q4W	Q2W: $-$66% to $-$75% versus placebo Q2W: $-$39.6% to $-$47.2% versus Eze Q4W: $-$63% to $-$75% versus placebo Q4W: $-$38.9% to $-$41.1% versus Eze	
DESCARTES, NCT01516879[89]	Fasting LDL-C $\geq$75 mg dL^{-1}	52 weeks	Diet Diet + Atorva 10 mg Diet + Atorva 80 mg Diet + Atorva 80 + Eze 10	420 mg Q4W	$-$57.0% (48.5-61.6) versus placebo	
GLAGOV, NCT01813422	Fasting LDL-C $\geq$80 mg dL^{-1}	78 weeks	Stable LLT therapy	Evo Q4W (dose not specified)	Ongoing (2016)	Nominal change in percent atheroma volume
GAUSS, NCT01375764[90]	Statin-intolerant	12 weeks	Stable LLT therapy (including statin or low-dose statin)	280, 350, or 420 mg Q4W 420 mg Q4W + Eze 10	$-$26% to $-$35.9 versus Eze $-$47.3% versus Eze	
GAUSS-2, NCT01763905[91]	Statin-intolerant; subjects not at LDL-C goal	12 weeks	Not on statin or on low-dose statin	140 mg Q2W 420 mg Q4W Eze 10	$-$38.1% versus Eze $-$37.6% versus Eze	
GAUSS-3, NCT01984424	Statin-intolerant; subjects not at LDL-C goal	Part A: Atorva rechallenge Part B: 24 weeks Part C: 2 years	Stable LLT for at least 4 weeks	Part A: Atorva rechallenge Part B: evo Q4W versus Eze Part C: evo Q2W		Percent change from baseline in LDL-C
FOURIER, NCT01764633	CVD at high risk for a recurrent event LDL-C $\geq$70 mg dL^{-1}	5 years	Effective statin therapy (Atorva 20 mg or equivalent)	140 mg Q2W + effective statin dose 420 mg Q4W + effective statin dose	Ongoing (2017)	Time to CV death, MI, hospitalization for UA, stroke, or coronary revascularization
RUTHERFORD, NCT01375751[92]	HeFH; fasting LDL-C $\geq$100 mg dL^{-1}	12 weeks	Statin $\pm$ ezetimibe	350 mg Q4W 420 mg Q4W	$-$43.8% versus placebo $-$56.4% versus placebo	

(Continued)

Table 2 Results from clinical trials on evolocumab—cont'd

Clinical trial (ClinicalTrials.gov identification number)	*Subjects*	*Duration*	*Background LLT*	*Intervention*	*LDL-C (percent change from baseline)*	*Primary end point for ongoing trials*
RUTHERFORD-2, NCT01763918[93]	HeFH; fasting LDL-C $\geq$100 mg dL^{-1}	12 weeks	Statin $\pm$ ezetimibe	140 mg Q2W 420 mg 04 W	$-$59.2% versus placebo $-$61.3% versus placebo	
TESLA part A, NCT01588496[94]	HOFH; LDL-C $\geq$130 mg dL^{-1}	36 weeks	Stable LLT for at least 4 weeks	420 mg Q4W for 24 weeks + 420 mg Q2W for 12 weeks	Q4W: $-$16.5% Q2W: $-$13.9%	
TESLA part B, NCT01588496[95]	HoFH; LDL-C $\geq$130 mg dL^{-1}	12 weeks	Stable LLT for at least 4 weeks	420 mg Q4W	$-$30.9% versus placebo	
TAUSSIG, NCT01624142	Severe FH	5 years	Stable LLT	Evo Q2W or Q4W	Ongoing (2020)	Subject incidence of treatment-emergent adverse events
OSLER-1, NCT01439880[96]	Subjects from phase 2 evolocumab trials	1 year		420 mg Q4W + standard therapy	$-$58.4% at week 48 versus standard therapy	Subject incidence of treatment-emergent adverse events
OSLER-2, NCT01854918[97]	Subjects from phase 3 evolocumab trials	1 year			Ongoing (2018)	

FH, familial hypercholesterolemia; *HeFH*, heterozygous familial hypercholesterolemia; *HoFH*, homozygous familial hypercholesterolemia; *LLT*, lipid-lowering therapy; *Q2W*, every 2 weeks; *Q4W*, every 4 weeks; *Eze*, ezetimibe.

in 3.1% taking ezetimibe.[90] In the phase 3 *GAUSS-2* study (NCT01763905), effects of evolocumab 140 mg Q2W or 420 mg Q4W compared with ezetimibe daily were evaluated in hypercholesterolemic patients intolerant to statins and with LDL-C above the recommended target.[91] After a 12-week treatment, evolocumab significantly reduced LDL-C levels compared with ezetimibe ($-$56.1% with evolocumab 140 mg Q2W and $-$52.6% with evolocumab 420 mg Q4W, compared with $-$18.1/$-$15.1% with ezetimibe), with no difference between the two different evolocumab regimens.[91] Similar results were obtained when considering other biochemical parameters, including non-HDL-C, apoB, and Lp(a).[91] More patients treated with evolocumab reached the LDL-C target goals compared with ezetimibe.[91] Myalgia occurred in 8% of evolocumab patients and 18% of ezetimibe patients.[91] The benefit of evolocumab on CV outcomes is currently under investigation in the GAUSS-3 and the FOURIER (*Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk*) studies. The *GAUSS-3* trial (NCT01984424) will include a placebo-controlled reexposure to statin (atorvastatin) before a 24-week double-blind comparison of evolocumab and ezetimibe, followed by 2-year open-label evolocumab extension (**Table 2**). The *FOURIER* study (NCT01764633) will evaluate the effect of evolocumab added to other treatments for dyslipidemia on the risk of CV death, MI, hospitalization for unstable angina, stroke, or coronary revascularization (**Table 2**).

Despite currently used drugs improving the management of HeFH patients, they often do not achieve their LDL-C level target; thus, the *RUTHERFORD* (*Reduction of LDL-C with PCSK9 Inhibition in Heterozygous Familial Hypercholesterolemia Disorder*, NCT01375751) trial evaluated whether evolocumab 350 or 420 mg Q4W was effective in HeFH patients who were unable to achieve LDL-C $<$100 mg dL^{-1} ($<$2.6 mmol L^{-1}) despite statin therapy with or without ezetimibe.[92] Percentage reductions of LDL-C were $-$43.8% and $-$56.4% versus placebo, respectively[92] (**Table 2**); when compared with patients on ezetimibe or statin alone, similar reductions versus placebo were observed.[92] At week 12, 70% and 89% of patients treated with 350 and 420 mg evolocumab reached LDL-C levels $<$100 mg dL^{-1} ($<$2.6 mmol L^{-1}) and 44% and 65% reached LDL-C $<$70 mg dL^{-1} ($<$1.8 mmol L^{-1}).[92] Overall, lipid profile was significantly improved, with TC, non-HDL-C, apoB, and Lp(a) significantly reduced.[92] The last finding has a special relevance for FH patients, who commonly exhibit elevated Lp(a) levels. Adverse events were similar in evolocumab-treated patients and in placebo group.[92] The phase 3 *RUTHERFORD-2* (NCT01763918) trial showed that administration of evolocumab 140 mg Q2W or 420 mg Q4W results in similar reductions of LDL-C levels after a 12-week treatment ($-$59.2% and $-$61.3% vs. placebo, respectively)[93] (**Table 2**). Reductions were not related to sex, age, body mass index, or type of therapy (intensity of statin therapy or concomitant use of ezetimibe).[93] Among the patients who participated in this study, seven were found to be HoFH or compound heterozygous following the genetic analysis, although they were initially classified as HeFH.[93] They exhibited higher baseline LDL-C levels compared with HeFH, but LDL-C reductions were 68% with 140 mg Q2W and 48% with 420 mg Q4W,[93] which is a much greater response than those reported in trials with selected patients with HoFH. In the pilot study *TESLA* (*Trial Evaluating PCSK9 Antibody in Subjects with LDL Receptor Abnormalities*, NCT01588496) *part A*, eight patients with HoFH (six LDLR-defective and two LDLR-negative) were treated with evolocumab 420 mg Q4W for 24 weeks, followed by 420 mg Q2W for an additional 12 weeks.[94] The treatment resulted in a mean reduction of LDL-C of 17%, with four patients experiencing reductions above 15% and three experiencing reductions above 30%[94] (**Table 2**); the two LDLR-negative patients did not show a reduction of LDL-C levels.[94] In the *TESLA part B*, patients with HoFH not receiving apheresis were administered evolocumab 420 mg or placebo

(33 and 16, respectively) Q4W for 12 weeks in addition to their current lipid-lowering therapy.[95] Evolocumab administration resulted in a reduction versus placebo of 30.9%; one LDLR-negative patient and one patient with autosomal recessive hypercholesterolemia did not respond to the treatment.[95] Among the patients homozygous for the same LDLR mutation, LDL-C reductions were highly heterogeneous and varied from −7.1% to −56%.[95] Overall, the response to evolocumab was related to the genetic defect determining HoFH and ranged from 0% in LDLR-negative patients to 40.8% in more than half of the patients carrying one or two defective LDLR mutations. Patients who completed this study were included in the one-arm open-label extension *TAUSSIG* (*Trial Assessing Long-Term Use of PCSK9 Inhibition in Subjects with Genetic LDL Disorders*, NCT01624142). This study will evaluate the long-term (5 years) efficacy and safety of evolocumab 420 mg Q4W or Q2W in a large cohort (100) of patients with HoFH and has a completion date in March 2020 (**Table 2**). Preliminary data (http://www.athero.org/isa2015/ClinicalBreak/Raal.pdf) show that the reduction of LDL-C persisted up to week 48 and that the administration Q2W results in an incremental 6% reduction compared with evolocumab Q4W in patients not receiving apheresis.

OSLER-1 and *OSLER-2* (*Open-Label Study of Long-Term Evaluation against LDL-C*, NCT01439880 and NCT01854918) are open-label extension trials involving heterogeneous groups of patients that participated in one or more phase 2 or phase 3 studies, respectively, on evolocumab.[96] After 11.1 months, evolocumab reduced LDL-C levels by 61% (**Table 2**).[96] The OSLER-1 study showed that a major part of patients who received evolocumab achieved LDL-C levels below those recommended by current guidelines, with a high percentage of subjects reaching LDL-C levels $<50\ mg\ dL^{-1}$ ($1.3\ mmol\ L^{-1}$), especially when evolocumab was coadministered with statins.[97] Adverse events, as well as serious adverse events, were similar in placebo- and evolocumab-treated patients.[96,97]

Alirocumab. Alirocumab has a half-life of 6–8 days and is administered subcutaneously every 2 or 4 weeks. In healthy volunteers, alirocumab significantly reduced LDL-C (>65%) and was well tolerated.[98] Three phase 2 trials have evaluated the effects of alirocumab in subjects with hypercholesterolemia. In hypercholesterolemic subjects on stable atorvastatin therapy (*Efficacy and Safety Evaluation of Alirocumab (SAR236553/REGN727) in Patients with Hypercholesterolemia on Stable Atorvastatin Therapy*, NCT01288443), alirocumab when administered for 12 weeks induced a further dose-dependent reduction of LDL-C levels, and the higher efficacy was observed with the Q2W administration compared with higher doses given Q4W[99] (**Table 3**); patients who were not at LDL-C target under atorvastatin therapy achieved this goal after alirocumab treatment.[99] TC, non-HDL-C, and apoB were also significantly reduced.[99] Adverse effects did not differ among groups.[99] Similar results were observed when alirocumab was added to low-dose (10 mg) or high-dose (80 mg) atorvastatin for 8 weeks (*Efficacy and Safety Evaluation of Alirocumab (SAR236553/REGN727) when Coadministered with Atorvastatin in Patients with Primary Hypercholesterolemia*, NCT01288469): a considerable decrease of LDL-C was observed following alirocumab administration compared with atorvastatin alone (−66.2%, −73.2%, and −17.3%, respectively) (**Table 3**), and a greater percentage of patients receiving alirocumab + atorvastatin 80 mg reached the LDL-C target level of $<100\ mg\ dL^{-1}$ ($<2.6\ mmol\ L^{-1}$) or $<70\ mg\ dL^{-1}$ ($<1.8\ mmol\ L^{-1}$), without specific safety issues.[100] When tested in a population of HeFH on statin with or without ezetimibe (*Study on the Safety and Efficacy of REGN727/SAR236553 in Patients with HeFH Hypercholesterolemia*, NCT01266876), alirocumab 150 mg Q2W (12-week treatment) reduced LDL-C by 67.9% compared with 10.65% of placebo[101] (**Table 3**).

The *ODYSSEY* program includes 14 phase 3 trials on alirocumab, among a large number of patients (>23,500) aimed at evaluating the efficacy and safety of alirocumab alone or when combined with other lipid-lowering therapies in several groups of hypercholesterolemic patients. Most of these trials use a dosage of 75 mg Q2W, which is uptitrated to 150 Q2W if the LDL-C target is not reached after 8 weeks. The *ODYSSEY COMBO* studies (I and II) evaluated the efficacy and safety of alirocumab as add-on therapy to stable, maximal tolerated dose of statin, with/without other lipid-lowering drugs in hypercholesterolemic patients of high CV risk. The *COMBO I* trial (*Efficacy and Safety of Alirocumab (SAR236553/REGN727) versus Placebo on Top of Lipid-Modifying Therapy in Patients with High Cardiovascular Risk and Hypercholesterolemia*, NCT01644175) showed that after 24 weeks, LDL-C decreased from baseline by −48.2% with alirocumab and by −2.3% with placebo, and the achieved LDL-C levels were comparable at weeks 24, 36, and 52[102] (**Table 3**); 75% of patients on alirocumab achieved the LDL-C target $<70\ mg\ dL^{-1}$ ($<1.8\ mmol\ L^{-1}$), compared with 9% of placebo.[102] The incidence of adverse effects was comparable in the two groups.[102] The *COMBO II* trial (*Efficacy and Safety of Alirocumab (SAR236553/REGN727) versus Ezetimibe on Top of Statin in High Cardiovascular Risk Patients with Hypercholesterolemia*, NCT01644188) compared the effect of alirocumab and ezetimibe in a 104-week treatment period in patients with high CV risk and high LDL-C levels despite maximal dose of statin.[103] Mean LDL-C levels decreased rapidly in the first 4 weeks; at week 24, percent change from baseline in LDL-C was −50.6% with alirocumab and −20.7% with ezetimibe (difference between groups: −29.8%) (**Table 3**); these values were maintained up to 52 weeks.[103] Similar incidences of adverse events were observed in the two groups.[103]

In *ODYSSEY FH* studies (FH I, FH II, and HIGH FH), alirocumab was evaluated in the HeFH population.[104] *ODYSSEY FH I* (performed in North America, Europe, and South Africa, NCT01623115) and *FH II* (performed in Europe, NCT01709500) studies, in which patients received alirocumab 75 mg Q2W uptitrated to 150 mg when LDL-C was $\geq 70\ mg\ dL^{-1}$ ($\geq 1.8\ mmol\ L^{-1}$) at week 8, showed that HeFH patients with LDL-C levels above the recommended target despite maximal tolerated dose of statin may greatly benefit from alirocumab treatment. In fact, at week 24, LDL-C levels were reduced by 57.9% (FH I) and 51.4% (FH II) versus placebo, respectively (**Table 3**), and these reductions were maintained through week 78.[105] The *ODYSSEY HIGH FH* (NCT01617655) was performed in patients with HeFH with LDL-C $\geq 160\ mg\ dL^{-1}$ ($\geq 4.1\ mmol\ L^{-1}$) and treated with alirocumab 150 mg Q2W or placebo for 78 weeks.[104] At week 24, in patients treated with alirocumab, LDL-C levels were reduced by 39% compared with placebo (**Table 3**).

ODYSSEY OPTIONS (I and II) studies were designed to evaluate the efficacy and safety of alirocumab with various therapeutic choices in patients at high CV risk with LDL-C levels not adequately controlled with atorvastatin 20 or 40 mg daily (OPTIONS I) or

Table 3 Results from clinical trials on alirocumab

Clinical trial (ClinicalTrials.gov)	*Subjects*	*Duration*	*Background LLT*	*Treatments*	*LDL-C (percent change from baseline)*	*Primary end point for ongoing trial·*
DFI11565, NCT01288443[99]	LDL-C $\geq$100 mg dL^{-1}	12 weeks	Atorva 10, 20, or 40 mg	Q2W: 50, 100, 150 mg Q4W: 200, 300 mg placebo	Q2W: −39.6% to −72.4% Q4W: −43.2%, −47.7%, −5.1%	
DFI11S66, NCT01288469[100]	LDL-C $\geq$100 mg dL^{-1}	8 weeks	Atorva 10 mg	150 mg Q2W ± Atorva 10 150 mg Q2W + Atorva 80 Atorva 80	−66.2%, −73.2%, −17.3%	
R727-CL-1003, NCT01266876[101]	HeFH; LOL-C $\geq$100 mg dL^{-1}	12 weeks	Diet + statin	150 Q2W 150, 200, 300 Q4W	−57.2% versus placebo −18.2% to −31.9% versus placebo	
ODYSSEY COMBO I, NCT01644175[102]	Established CHD or CUD equivalent, LDL-C $\geq$70 mg dL^{-1}	52 weeks	Max tolerated statin ± other LLT	75 mg Q2W (increased at 150 mg Q2W if LDL-C 270 mg dL^{-1} at week 8)	−45.9% versus placebo at week 24	
ODYSSEY COMBO II, NCT01644188[103]	Established CHD or CHD equivalent, LDL-C $\geq$70 mg dL^{-1} with maximally tolerated dose of statin	52 weeks	High-intensity statins	75 mg Q2W (increased at 150 mg Q2W if LDL-C $\geq$70 mg dL^{-1} at week 8)	−29.8% versus Eze at week 24 −31.2% versus Eze at week 52	
ODYSSEY FH I and FH II, NCT01623115 and NCT01709500[105]	HeFH, LDL-C $\geq$100 mg dL^{-1} (for primary prevention) or LDL-C $\geq$70 mg dL^{-1} (for secondary prevention)	78 weeks	Max tolerated statin ± other LLT	75 mg Q2W (increased at 150 mg Q2W if LDL-C $\geq$70 mg dL^{-1} at week 8)	FH I: −57.9% versus placebo FH II: −51.4% versus placebo	
ODYSSEY HIGH FH, NCT01617655[104]	HeFH LDL-C $\geq$160	78 weeks	Stable LLT	150 mg Q2W	−39% versus placebo at week 24	
ODYSSEY OPTIONS I, NCT01730040[107]	Very high CVD risk and LDL-C $\geq$70 mg dL^{-1} or high CVD risk and LDL-C $\geq$100 mg dL^{-1}	24 weeks	Atorva 20 or 40 mg	75 mg Q2W Eze 10 mg Doubling Atorva dose Atorva 40 → Rosuva 40	Entry statin: Atorva 20 (−44.1%, −20.5%); Atorva 40 (−54%, −22.6%, −21.4%)	
ODYSSEY OPTIONS II, NCT01730053[108]	Very high CVD risk and LDL-C $\geq$70 mg dL^{-1} or high CVD risk and LDL-C $\geq$100 mg dL^{-1}	24 weeks	Rosuva 10 or 20 mg	75 mg Q2W Eze 10 mg Doubling Rosuva dose	Entry statin: Rosuva 10 (−50.6%, −14.4%, −16.3%); Rosuva 20 (−36.3%, −11.0%, −15.9%)	
ODYSSEY ALTERNATIVE, NCT01709513[109]	Moderate or high CV risk with statin intolerance, LDL-C $\geq$100 or $\geq$70 mg dL^{-1}	24 weeks	Nonstatin LLT	75 mg Q2W Eze 10 mg	−34.7% versus Eze	
ODYSSEY MONO, NCT01644474[110]	LDL-C $\geq$100 and $<$190 mg dL^{-1}	24 weeks	None	75 mg Q2W Eze 10 mg	−31.6% versus Eze	
ODYSSEY LONG TERM, NCT01507831[111]	HeFH or established CHD or CHD equivalent LDL-C $\geq$70 mg dL^{-1}	78 weeks	Max tolerated statin ± other LLT	150 mg Q2W	−61.9% versus placebo at week 24	

Table 3 Results from clinical trials on alirocumab—cont'd

Clinical trial (ClinicalTrials.gov)	*Subjects*	*Duration*	*Background LLT*	*Treatments*	*LDL-C (percent change from baseline)*	*Primary end point for ongoing trial·*
ODYSSEY OLE, NCT01954394	HeFH who have completed one of the four parent studies	176 weeks			Ongoing (2017)	Assessment of safety parameters
ODYSSEY OUTCOMES, NCT01663402[112]	Recent ACS (4–52 weeks prior to randomization), LDL-C $\geq$70 mg dL^{-1}	64 months	Atorva 40–80 mg or Rosuva 20–40 or the max tolerated dose	75 mg Q2W 150 mg Q2W	Ongoing (2017)	Time from randomization to first occurrence of CHD death, nonfatal MI, stroke, or UA requiring hospitalization

FH, familial hypercholesterolemia; *HeFH*, heterozygous familial hypercholesterolemia; *HoFH*, homozygous familial hypercholesterolemia; *CHD*, coronary heart disease; *CVD*, cardiovascular disease; *ACS*, acute coronary syndrome; *LLT*, lipid-lowering therapy; *Q2W*, every 2 weeks; *Q4W*, every 4 weeks; *Atorva*, atorvastatin; *Rosuva*, rosuvastatin; *Eze*, ezetimibe.

rosuvastatin 10 or 20 mg daily (OPTIONS II).[106] The *ODYSSEY OPTIONS I* (NCT01730040) trial was performed in patients with very high CVD risk and LDL-C $\geq$70 mg dL^{-1} ($\geq$1.8 mmol L^{-1}) or high CVD risk and LDL-C $\geq$100 mg dL^{-1} ($\geq$2.6 mmol L^{-1}) and compared the efficacy and safety of alirocumab 75 mg Q2W (switched to 150 mg Q2W if LDL-C target was not achieved after 12 weeks) added to atorvastatin 20 or 40 mg with several alternative approaches including adding ezetimibe, doubling atorvastatin dose, or switching from atorvastatin 40 mg to rosuvastatin 40 mg.[107] The addition of alirocumab resulted in the greatest reduction of LDL-C, being reduced by 44.1% and 54.0% with baseline atorvastatin 20 or 40 mg, respectively, by 20.5% and 22.6% after addition of ezetimibe, by 5.0% and 4.8% with doubled atorvastatin dose, and by 21.4% when switching from atorvastatin to rosuvastatin[107] (**Table 3**). A significantly higher proportion of patients receiving alirocumab achieved their LDL-C goals compared with the other treatments[107]; in addition, alirocumab induced a higher reduction of apoB, non-HDL-C, and Lp(a) levels compared with other treatments.[107] Treatment-emergent adverse events were comparable among groups.[107] The *ODYSSEY OPTIONS II* (NCT01730053) evaluated the addition of alirocumab on a background of rosuvastatin 10 or 20 mg in the same type of patients and showed a higher reduction of LDL-C levels with alirocumab ($-$50.6% and $-$36.3%, respectively) compared with the addition of ezetimibe ($-$14.4% and $-$11.0%) or doubling rosuvastatin dose ($-$16.3% and $-$15.9%) after 24 weeks[108] (**Table 3**). Again, similar percentages of treatment-emergent adverse events in the various treatment groups were observed.[108] These trials demonstrated that the addition of PCSK9 antibody achieves LDL-C goals in patients at high/very high CVD risk and not optimally controlled with conventional lipid-lowering treatments.

Statin-intolerant patients with moderate to very high CVD risk with LDL-C $\geq$190 mg dL^{-1} ($\geq$4.9 mmol L^{-1}) were treated with alirocumab 75 mg Q2W (with potential uptitration to 150 mg Q2W) or ezetimibe 10 mg day^{-1} or atorvastatin 20 mg day^{-1} (statin rechallenge; included only as control to define the appropriate patient population) for 24 weeks to evaluate percent change from baseline in LDL-C in the *ODYSSEY ALTERNATIVE* trial (NCT01709513). Alirocumab was superior to ezetimibe in reducing LDL-C levels throughout the study ($-$54.8% and $-$20.1% from baseline, respectively, at week 24, $P<0.0001$) (**Table 3**); a greater proportion of patients receiving alirocumab achieved the LDL-C goals relative to their CV risk compared with those receiving ezetimibe (41.9% vs. 4.4%).[109] TC, non-HDL-C, apoB, and Lp(a) were more significantly reduced with alirocumab than with ezetimibe.[109] Myalgia was the most common adverse event in all groups, but in the alirocumab group, the rate of muscle-related adverse events was significantly lower than in the atorvastatin group (hazard ratio: 0.61, $P=0.042$) with a similar result also compared with the ezetimibe group (HR 0.71, $P=0.096$).[109] Similar results were obtained in the *ODYSSEY MONO* trial (NCT01644474), conducted in hypercholesterolemic patients on no lipid-lowering therapy, with reductions of LDL-C levels of 47.2% with alirocumab and 15.6% with ezetimibe at week 24[110] (**Table 3**).

Two trials have been designed to evaluate the safety of long-term administration of alirocumab. The *ODYSSEY LONG TERM* (NCT01507831) was conducted in high CV risk patients with hypercholesterolemia not adequately controlled by the current lipid-lowering therapy and treated with alirocumab or placebo for up to 86 weeks. The mean percent change in calculated LDL-C was $-$61% with alirocumab and +0.8% with placebo at week 24[111] (**Table 3**) and was similar in HeFH and non-HeFH patients; a consistent reduction of LDL-C levels was obtained after a 4-week treatment and maintained up to 78 weeks.[111] Adverse events occurred similarly in the two groups, but myalgia occurred at a higher frequency in the alirocumab group (5.4% vs. 2.9% in placebo, $P=0.006$).[111] A post hoc analysis suggests a lower rate of major CV events in patients treated with alirocumab than in the placebo group (1.7% vs. 3.3%, HR 0.52, nominal $P=0.02$), with cumulative probability of event curves tending to diverge over time.[111] The ongoing *ODYSSEY OLE* (Open Label Study of Long-Term Safety Evaluation of Alirocumab) (NCT01954394) has as

current primary outcome the assessment of safety parameters (adverse events, laboratory data, and vital signs) following a treatment with alirocumab up to 176 weeks in patients with HeFH. Secondary outcomes are the effects on lipid parameters; the estimated completion date is June 2017.

Finally, the *ODYSSEY OUTCOMES* (NCT01663402) is recruiting patients with a recent acute coronary syndrome to evaluate the effect of adding alirocumab versus placebo to their current therapy on the occurrence of CV events, including CHD death, MI, fatal and nonfatal ischemic stroke, and unstable angina requiring hospitalization.[112]

Bococizumab. Four phase 2 trials on bococizumab have been performed (NCT01342211, NCT01592240, NCT01350141, and NCT02055976); to date, only results from one of these studies have been published. Ballantyne et al. showed that bococizumab (NCT01592240) significantly reduced LDL-C levels across all doses in patients with hypercholesterolemia on stable statin therapy and with fasting LDL-C $\geq$80 mg dL^{-1} ($\geq$2.1 mmol L^{-1})[113] (**Table 4**); however, despite similar reductions with low doses (100 and 150 mg) Q2W or high doses (200 and 300 mg) Q4W, patients who received bococizumab Q2W maintained the LDL-C reductions between dose administration, whereas those who received bococizumab Q4W did not.[113] The frequency of adverse events was similar in all groups.[113] The *SPIRE* (Studies on PCSK9 Inhibition and the Reduction of Vascular Events) program includes eight phase 3 trials (**Table 4**); among these, six are designed to assess the LDL-C-lowering efficiency of bococizumab in several hypercholesterolemic populations (SPIRE-AI, NCT02458287; SPIRE-SI, NCT02135029; SPIRE-FH, NCT01968980; SPIRE-LL, NCT02100514; SPIRE-HR, NCT01968954; and SPIRE-LDL, NCT01968967), whereas the other two will evaluate the effect of long-term bococizumab administration on the occurrence of major CV events in high-risk patients with LDL-C levels 70–100 mg dL^{-1} (1.8-2.6 mmol L^{-1}) (SPIRE-1: NCT01975376) or with LDL-C levels $\geq$100 mg dL^{-1} ($\geq$2.6 mmol L^{-1}) despite high-dose statin (SPIRE-2: NCT01975389).

7.18.3.1.3 Mipomersen

Despite the fact that statins are the most used LDL-C-lowering drug class, certain patients with FH may not benefit from the use of statins or PCSK9 mAbs because their mechanism of action requires the presence of at least partially functional LDLR.[8,9] Thus, HoFH with *ldlr* mutations leading to the absence of LDLR will not benefit from statin- or anti-PCSK9 mAb-based therapies and thus need

Table 4 Results from one clinical trial on bococizumab and list of the ongoing trials

Clinical trial (ClinicalTrials.gov identification number)	*Subjects*	*Duration*	*Background LLT*	*Treatments*	*LDL-C (percent change from baseline)*	*Primary end point for ongoing trials*
NCT01592240[113]	Fasting LDL-C $\geq$80 TG $\leq$400 mg dL^{-1}	24 weeks	Stable statin therapy	Q2W: 50, 100, 150 mg Q4W: 200, 300 mg	Q2W: −35.4%, −52.3%, −54.2% Q4W: −21.3%, −38.3%	
SPIRE-AI, NCT02458287	Hyperlipidemic/dyslipidemic LDL-C $\geq$70 mg dL^{-1} TG $\leq$400 mg dL^{-1}	12 weeks	Statin	75, 150 mg Q2W	Ongoing (2016)	Percent change from baseline in LDL-C
SPIRE-SI, NCT02135029	Hyperlipidemic, statin-intolerant LDL-C $\geq$70 mg dL^{-1} TG $\leq$400 mg dL^{-1}	24 weeks		150 mg Q2W	Ongoing (2015)	Percent change from baseline in fasting LDL-C
SPIRE-FH, NCT01968980	HeFH LDL-C $\geq$70 mg dL^{-1} TG $\leq$400 mg dL^{-1}	52 weeks	Statin	150 mg Q2W	Ongoing (2016)	Percent change from baseline in LDL-C
SPIRE-LL, NCT02100514	High or very high CV risk LDL-C $\geq$100 mg dL^{-1} TG $\leq$400 mg dL^{-1}	52 weeks	Statins	150 mg Q2W	Ongoing (2016)	Percent change from baseline in fasting LDL-C
SPIRE-HR, NCT01968954	High or very high CV risk LDL-C $>$70 mg dL^{-1} TG $\leq$400 mg dL^{-1}	12 months	Statin	150 mg Q2W	Ongoing (2016)	Percent change from baseline in LDL-C
SPIRE-LDL, NCT01968967	High or very high CV risk fasting LDL-C $>$70 mg dL^{-1} TG $\leq$400 mg dL^{-1}	12 months	Statin	150 mg Q2W	Ongoing (2016)	Percent change from baseline in LDL-C
SPIRE-1, NCT01975376	High CV risk LDL-C $\geq$70 and $<$100 mg dL^{-1}	5 years	LLT	150 mg Q2W	Ongoing (2018)	CV death, nonfatal MI or stroke, UA needing urgent revascularization
SPIRE-2, NCT01975389	High CV risk LDL-C $\geq$100 mg dL^{-1}	5 years	LLT	150 mg Q2W	Ongoing (2018)	CV death, nonfatal MI or stroke, UA needing urgent revascularization

HeFH, heterozygous familial hypercholesterolemia; *CV*, cardiovascular; *LLT*, lipid-lowering therapy; *Q2W*, every 2 weeks.

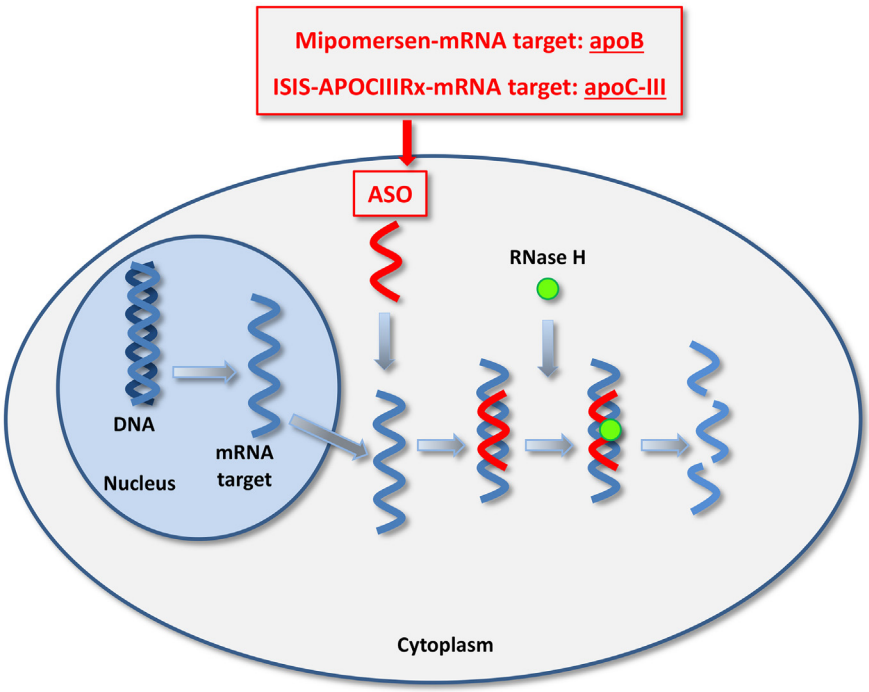

Fig. 4 Mechanism of action of antisense oligonucleotides. Mipomersen and ISIS-APOCIIIRx are second-generation antisense oligonucleotides (ASOs) that inhibit the synthesis of apoB and apolipoprotein C-III, respectively. They bind to the cognate mRNA forming a substrate for ribonuclease H (RNase H), a ubiquitously expressed nuclease, thus resulting in mRNA degradation and reduced production of the encoded protein.

alternative lipid-lowering drugs with mechanisms of action independent of LDLR expression as add-on to the maximal potent statin dose[8] and may include ezetimibe and the most recently approved mipomersen and lomitapide.[9]

High levels of apoB, the main apoprotein of atherogenic lipoproteins [LDL, very-low-density lipoprotein (VLDL), and chylomicrons], represent an established risk factor in atherosclerosis, and the discovery of truncating apoB mutations resulting in low levels of LDL-C indicated it as potential pharmacological target for the treatment of hypercholesterolemia.[114] Mipomersen is a second-generation antisense oligonucleotide (ASO) against the coding region of human apoB mRNA and thus acts as an inhibitor of apoB synthesis[115] (**Fig. 4**). When administered by injection, it is rapidly absorbed, with the liver being one of the organs that accumulate the highest concentrations of this drug,[115] and in humans, it has an elimination half-life of about 30 days.[115] Its administration leads to a dose-dependent reduction of apoB and TC [116]; several studies have shown the lipid-lowering efficacy of mipomersen either as monotherapy or as add-on to current lipid-lowering therapies.[117–124] Mipomersen is not metabolized by the CYP450 system, it does not inhibit major CYP isoenzymes, and it does not show clinically relevant interaction with simvastatin or ezetimibe.[125] The most common adverse reaction associated with mipomersen is the injection site reaction following subcutaneous administration. Due to its characteristics, mipomersen represents an effective approach as lipid-lowering agent in the management of FH but can also be considered in statin-intolerant patients.

Two meta-analyses of randomized clinical trials have reported significant decrease of LDL-C levels induced by mipomersen treatments, as well as beneficial effects on other lipid parameters.[126,127] Both meta-analyses reported as major adverse events associated with mipomersen treatment the risk of injection site reactions, elevated alanine aminotransferase (ALT) $>3\times$ the upper limit of normal (ULN), and hepatic steatosis and flu-like symptoms;[126,127] the most relevant side effect of mipomersen seems to be an increased content of TG in the liver, but though short-term studies revealed an increased steatosis (whose clinical relevance was considered low) in mipomersen-treated subjects, long-term (up to 104 weeks) clinical trials observed a return to normal of hepatic TG level.[128,129] The analysis of liver biopsies of some hypercholesterolemic patients after mipomersen treatment showed a histopathological feature of simple steatosis without signs of inflammation or fibrosis.[130]

In the *ASSIST* (Safety and Efficacy Study of ISIS 301012 (Mipomersen) Administration in High Risk Subjects NCT00707746) trial, mipomersen (200 mg $week^{-1}$) significantly decreased apoB100 and LDL-C levels and reduced small dense proatherogenic LDL, but did not affect high-density lipoprotein (HDL) or apoA-I levels in statin-intolerant hypercholesterolemic patients[124] (**Table 5**); overall, mipomersen was well tolerated.[124] In patients with mild to moderately elevated LDL-C (*Safety and Tolerability of Varying Load and Dose of ISIS 301012 in People with Elevated LDL-C Levels*, NCT00216463) (130 mg dL^{-1} and 3.3 mmol L^{-1}) who did not receive any lipid-lowering therapy in the past month, mipomersen at doses ranging from 50 to 400 mg $week^{-1}$ dose-dependently reduced LDL-C levels (from -8% to -70.6%)[123] (**Table 5**). In hypercholesterolemic patients at high CV risk (*Safety and Efficacy of Mipomersen (ISIS 301012) as Add-on Therapy in High Risk Hypercholesterolemic Patients*, NCT00770146), mipomersen 200 mg significantly reduced LDL-C levels (**Table 5**); after treatment completion, LDL-C levels increased and reached

Table 5 Results from clinical trials on mipomersen and lomitapide

Clinical trial (ClinicalTrials.gov identification number)	*Subjects*	*Duration*	*LDL-C (percent change from baseline)*	*Lp(a) (percent change from baseline)*	*Primary end point for ongoing clinical trials*
Mipomersen					
ASSIST (NCT00707746)[124]	Statin-intolerant, hypercholesterolemic at high CVD risk	26 weeks	−47.3% (200 mg) (vs. −2% placebo)	−27.1% (200 mg) (vs. 0% placebo)	
NCT00216463[123]	LDL-C ≥130 mg dL^{-1}	13 weeks	−8% (50 mg) to 70.6% (400 mg) versus placebo		
NCT00770146[131]	LDL-C ≥100 mg dL^{-1}, at high CHD risk, on stable maximally tolerated dose of statin	28 weeks	−39.6% (200 mg) (−4.5% placebo)	−25.6% (200 mg) (vs. 0.0% placebo)	
NCT00477594[118]	HeFH	6 weeks	−13% (50 mg) to −34% (300 mg) versus placebo	−3% (50 mg) to −24% (300 mg)	
RADICHOL II, NCT00706849[122]	HeFH with CAD on maximally tolerated statin, LDL-C ≥100 mg dL^{-1}	28 weeks	−28% (200 mg) (vs. +5.2% placebo)	−21.1% (200 mg) (vs. +0.0% placebo)	
RADICHOL 1, NCT00607373[121]	HoFH	28 weeks	−21.1% (160 mg) versus placebo	−23.2% (160 mg) versus placebo	
NCT00694109[132]	FH or severe hypercholesterolemia	4.5 years	−28% at week 104	−14% at week 104	
FOCUS FH, NCT01475825	Severe HeFH	60 weeks			Percent change from baseline in LDL-C (completion date: 2016)
Lomitapide					
Cuchel etal.[145]	HoFH	4 weeks for each dose	−24.7% (0.3 mg) −50.9% (1.0 mg)	Unchanged	
NCT00730236[146]	HoFH	26+52 weeks	−50% at week 26 -38% at week 78	−15% at week 26 –0.5% at week 78	
Roeters van Lennep et al.[150]	HoFH		−35% to −73%		

CVD, cardiovascular disease; *CHD*, coronary heart disease; *CAD*, coronary artery disease; *HeFH*, heterozygous familial hypercholesterolemia; *HoFH*, homozygous familial hypercholesterolemia.

baseline levels after 24 weeks.[131] The effect appeared to be greater in women and in patients aged >59 years.[131] Other lipid parameters, including Lp(a), were significantly reduced by mipomersen treatment.[131] All patients treated with mipomersen experienced an injection site reaction, while 23% had an ALT elevation >3× ULN.[123] In a phase 2 study (NCT00477594), 44 patients with HeFH were randomized to mipomersen 50, 100, 200, or 300 mg $week^{-1}$ or placebo for 6 weeks in a background of conventional lipid-lowering therapy, including high-dose statins. Mipomersen reduced apoB and LDL-C by 23% and 21%, respectively, at 200 mg $week^{-1}$ and by 33% and 34%, respectively, at 300 mg $week^{-1}$[118] (Table 5). The most common adverse effect with mipomersen was injection site erythema (97%); four patients treated with mipomersen (three of which in the highest dose group) experienced transaminase elevations >3× ULN with signs of hepatic steatosis; no clinically relevant interactions with currently used drugs were observed.[118] LDL-C levels remained lower than baseline levels for 2–3 months after the last injection in the two groups with the highest doses (200 and 300 mg $week^{-1}$), likely due to the long mipomersen half-life.[118] In HeFH patients with CAD (*RADICHOL II*: *Efficacy and Safety Study of ISIS 301012 (Mipomersen) as Add-on in Familial Hypercholesterolemic Patients with Coronary Artery Disease*, NCT00706849), mipomersen treatment induced a −28% reduction from baseline in LDL-C (vs. +5.2% placebo, $P<0.001$) (Table 5); the reduction was independent of baseline LDL-C levels and age, but the response was greater in women than in men.[122] ApoB, non-HDL-C, TC, and Lp(a) were significantly reduced in the mipomersen group.[122]

Effective LDL-C reduction with mipomersen (200 mg $week^{-1}$ for 26 weeks) was observed also in 51 patients with HoFH already treated with maximal conventional lipid-lowering therapy (*RADICHOL 1*: *Study to Assess the Safety and Efficacy of ISIS 301012 (Mipomersen) in Homozygous Familial Hypercholesterolemia*, NCT00607373): the mean percent change in LDL-C from baseline was −24.7% (vs. −3.3% with placebo), independently of baseline LDL-C levels.[121] Significant reductions in apoB (−24.2%), non-HDL-C (−21.6%), and Lp(a) (−23.2%) were also reported.[121] Again, the most common adverse event was injection site reactions (76% of mipomersen patients and 24% of placebo patients).[121] ALT elevations ≥3 times ULN occurred in four mipomersen patients, including 1 who had significantly increased hepatic fat.[121] A recent report of 2-year interim results of an ongoing open-label study (conducted in patients with FH or severe hypercholesterolemia on lipid-lowering therapy who had completed one of the described studies, NCT00694109) (Table 5) showed that, in HoFH and HeFH patients, mipomersen in

combination with the maximally tolerated dose of lipid-lowering therapy showed that favorable effects on lipid profile were maintained throughout the study and that safety issues were similar to those reported for a 26-week treatment.[132] Data from the 4-year time point will further clarify this finding.

Besides its effect on LDL-C levels, mipomersen has been also evaluated on Lp(a) levels. Lp(a) is a causal, independent genetic risk factor for MI, stroke, and peripheral artery disease.[133–135] Its levels are particularly elevated in patients with FH and are related to severity of hypercholesterolemia,[136] and commonly used lipid-lowering drugs are not effective in reducing Lp(a). Lp(a) has a structure similar to that of LDL, from which it differs in the presence of the glycoprotein apolipoprotein (a) covalently bound to apoB.[137] As mipomersen acts by specifically inhibiting apoB production, it may also affect the formation of Lp(a). In four phase 3 trials, mipomersen significantly reduced Lp(a) levels in various hypercholesterolemic populations[138]; the highest effects were reported in HoFH and in patients with severe hypercholesterolemia at week 26 (−31.8% and −39.1%, respectively).[138] In the pooled analysis of all patients, including HeFH with CAD and hypercholesterolemic patients at high risk for CAD, LDL-C levels were reduced by 26.4%,[138] thus suggesting that mipomersen can efficiently reduce both LDL-C and Lp(a) levels. Whether this can translate into a further clinical benefit remains to be addressed, as the commonly used lipid-lowering drugs do not lower Lp(a).[139]

The ongoing *FOCUS FH* (*A Study of the Safety and Efficacy of Two Different Regimens of Mipomersen in Patients with Familial Hypercholesterolemia and Inadequately Controlled Low-Density Lipoprotein Cholesterol*, NCT01475825) study will determine whether administration of mipomersen for 60 weeks at two different dosing regimens (70 mg thrice weekly or 200 mg once weekly) can significantly reduce LDL-C levels in patients with severe HeFH, thus providing further information on the efficacy and safety of this drug.

7.18.3.1.4 Lomitapide

MTP (microsomal triglyceride transport protein) is a lipid transfer protein crucial for the assembly and secretion of apolipoprotein B-containing lipoproteins, including VLDL and chylomicrons (Fig. 5).[140] MTP localizes in the endoplasmic reticulum (ER) of hepatocytes and enterocytes and acts by transferring TG and cholesteryl esters from the ER membrane to the nascent apoB.[140] Since subjects carrying mutations of the gene encoding for MTP (*MTTP*) exhibit significantly reduced synthesis of VLDL and chylomicrons and increased apoB degradation, thus resulting in reduced circulating VLDL and LDL,[141] it has been hypothesized that inhibition of MTP might be a valuable approach to treat hypercholesterolemia in FH patients. MTP inhibition results in the reduction of both cholesterol and TG plasma levels, due to the inhibition of production of apoB-containing lipoproteins in both the liver (VLDL) and intestine (chylomicrons). Studies in animal models of HoFH have in fact showed that MTP inhibition normalized the levels of atherogenic lipoproteins by greatly reducing the secretion rate of VLDL.[142–144]

Lomitapide is an MTP inhibitor that, by binding MTP, inhibits MTP-mediated synthesis of VLDL and chylomicrons, thus resulting in a significant reduction of LDL-C levels (Fig. 5). Due to the high difficulty to efficiently treat HoFH patients, lomitapide

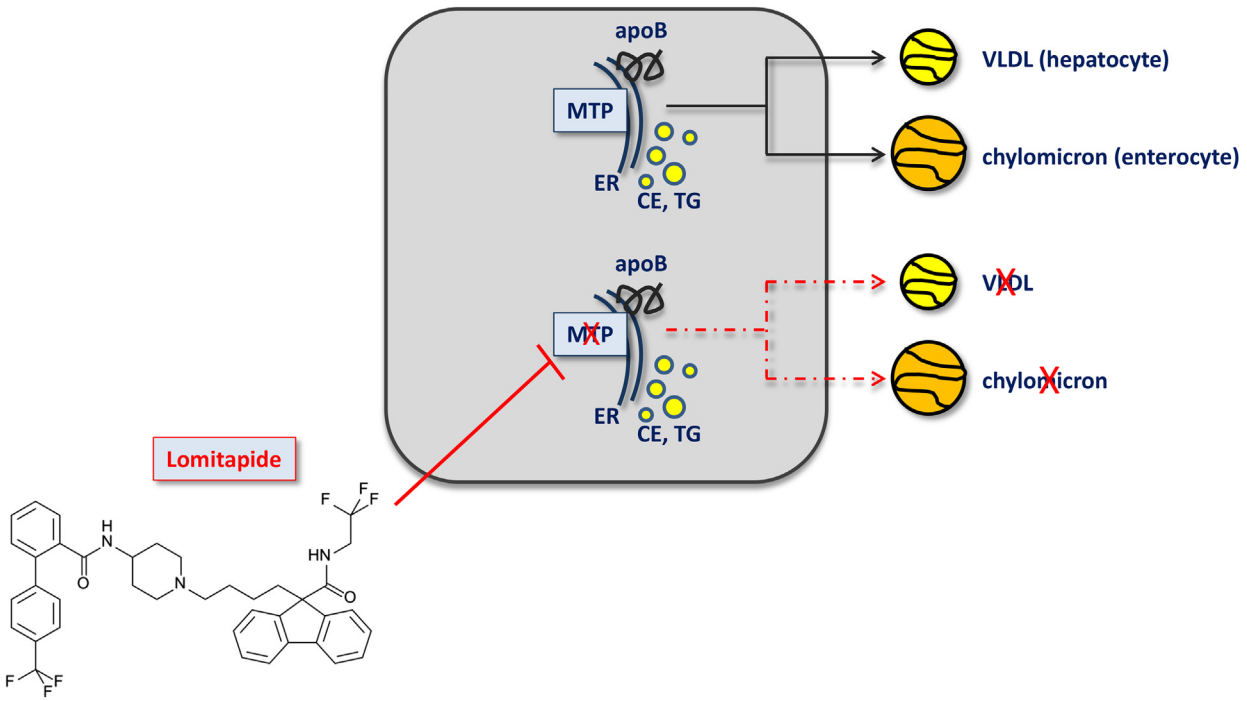

Fig. 5 Mode of action of lomitapide. MTP mediates the transfer of lipid droplet to apoB-100 in the liver and apoB-48 in the intestine, thus resulting in the secretion of VLDL and chylomicrons, respectively. Lomitapide inhibits the activity of MTP in both the liver and intestine.

was considered as a possible approach to reduce LDL-C levels in these patients; to test this possibility, six patients with HoFH (five LDLR-negative and one LDLR-defective) were enrolled in a study in which all lipid-lowering treatments were suspended at least 4 weeks before the baseline visit, and lomitapide was administered at four increasing doses (0.03, 0.1, 0.3, and 1.0 mg kg^{-1} body weight), each for 4 weeks.[145] The mean LDL-C level was reduced by 24.7% after 0.3 mg kg^{-1} for 4 weeks and by 50.9% after 1.0 mg kg^{-1} for 4 weeks[145] (Table 5); similarly, TC was reduced by 29.8% and 58.4% from the baseline level, respectively.[145] Both TG and apoB were significantly reduced (TG, −34.1% and −65.2%, and apoB, −14.7% and −55.6%, respectively).[145] The drug was well tolerated and the most serious adverse events were elevations in liver aminotransferase levels and hepatic fat accumulation.[145] Thus, lomitapide was highly effective in reducing LDL-C levels, but the accumulation of fat in the liver requires further investigations to evaluate the long-term safety.

To answer this question, lomitapide was given to 29 HoFH patients in single-arm, open-label, phase 3 study in addition to their lipid-lowering therapy (*A Safety and Efficacy Study of AEGR-733 to Treat Homozygous Familial Hypercholesterolemia*, NCT00730236).[146] This study consisted of a 26-week efficacy study during which lomitapide was initiated at a starting dose of 5 mg day^{-1} for the first 2 weeks and then escalated to 10, 20, 40, and 60 mg day^{-1} at 4-week intervals or until the maximal dose was identified for each subject on the basis of safety and tolerability, and a 52-week safety study that allowed the investigators to modify the concomitant lipid-lowering therapy based on lomitapide effect.[146] Mean LDL-C levels were significantly reduced by 50% at the end of efficacy phase, leading to the discontinuation of LDL apheresis or to the increased interval times between two apheresis processes.[146] At the end of the study (week 78), LDL-C was still significantly reduced, but the reduction was attenuated (−38%) compared with the values at the end of the efficacy study (Table 5); this could be due to changes in the concomitant lipid-lowering therapies as well as to the reduction of lomitapide doses in patients experiencing adverse effects.[146] Very-low-density lipoprotein cholesterol (VLDL-C), non-HDL-C, and TG levels were significantly decreased at the end of the efficacy phase (−45%, −50%, and −45%, respectively), and at the end of the study, such reductions resulted attenuated (−31%, −39%, and −31%, respectively), in line with the results obtained for LDL-C levels (Table 4).[146] HDL-C and apoA-I levels were significantly reduced at week 26 (−12% and −14%), but returned to levels similar to baseline at the end of the study.[146] During the first period (0–26 weeks), 15 patients reached the LDL-C level target <100 mg dL^{-1} (2.6 mmol L^{-1}), and 8 had LDL-C <70 mg dL^{-1} (<1.8 mmol L^{-1}).[146] The effect of lomitapide on LDL-C level was independent of apheresis treatment, as comparable reductions of LDL-C levels were achieved in patients undergoing apheresis and in those not undergoing apheresis (55.1% vs. 48%).[147] Most patients had mild to moderate gastrointestinal adverse effects during the treatment with lomitapide. Some patients exhibited increased levels of ALT, aspartate aminotransferase (AST), or both, but these changes were transient, were resolved when lomitapide doses were reduced, and were not related to changes of liver function.[146] Mean hepatic fat increased during the efficacy phase but did not further increase (8.6% at week 26 and 8.3% at week 78).[146] The clinical relevance of this rise in liver fat is still unclear and, since lomitapide might be administered lifelong, requires further investigation to assess whether it can progress to hepatic fibrosis or cirrhosis. Comparable results were reported in an Italian subgroup of HoFH patients participating in the described study.[148] These findings, together with the recent data obtained in a HoFH patient treated with lomitapide in addition to other lipid-lowering therapies for 5 years,[149] suggest that lomitapide may be a valuable pharmacological approach for the treatment of these very high-risk patients.

Recently, the use of lomitapide in four HoFH patients (two compound heterozygotes and two homozygotes) in the clinical practice setting has been reported.[150] In all patients, LDL-C levels were significantly reduced (35–73%)[150] (Table 5). One compound heterozygous patient having two different severe mutations in the *LDLR* gene, one in each allele, who had LDL-C levels ranging from 290 to 688 mg dL^{-1} (7.4–17.6 mmol L^{-1}) despite atorvastatin + colesevelam therapy, was treated with lomitapide. Lomitapide was started at 5 mg and then escalated to 30 mg day^{-1}; LDL-C levels decreased drastically, reaching very low levels (93 mg dL^{-1} and 2.4 mmol L^{-1}), with a reduction of 83% over 8 months.[150] The second compound heterozygote who had an LDL-C level of about 260 mg dL^{-1} (6.7 mmol L^{-1}) when lomitapide was added to the maximal background LLT (rosuvastatin 40 mg, ezetimibe 10 mg, and colesevelam 2.5 g) had LDL-C reduced by 35%.[150] In one HoFH LDLR-negative patient, who underwent apheresis and was on simvastatin + ezetimibe therapy, lomitapide therapy resulted in LDL-C and TC reductions of 73% and 62%, respectively.[150] The other homozygous patient who had a history of CV disease started lomitapide 5 mg and had a significant decrease of LDL-C within 1 month of treatment.[150] However, when escalated to 10 mg daily, levels of AST and ALT increased by more than 5× ULN, which resulted in the discontinuation of the drug. Resumption of lomitapide after 4 weeks at 5 mg also increased ALT by three times; thus, the drug was stopped permanently.[150] Altogether, these data indicate that, although lomitapide added to aggressive lipid-lowering therapies may be useful to further reduce LDL-C in HoFH, each patient must be individually monitored to avoid hepatic impairment. Longer follow-ups are required to establish whether lomitapide treatment may effectively prevent CV events.

To date, there are few data on the long-term efficacy and safety of lomitapide. A single case report has been published regarding a patient with a homozygosity for *LPL* gene resulting in the production of noncatalytically active enzyme associated with severe hypertriglyceridemia (HTG) and recurrent pancreatitis.[151] In 1999, lomitapide was given to this patient after stopping all other lipid-lowering treatments; fasting TG levels were significantly reduced, and in the course of 13 years, she had three hospitalizations for pancreatitis during discontinuation of lomitapide or high dietary fat intake.[151] Plasma levels of ALT and AST were within the reference range during the initial 6–7 years and then increased; the fatty liver that was already present before starting lomitapide progressed to hepatitis and fibrosis.[152] It is possible that inhibition of MTP may have reduced the main route by which hepatocytes reduce their fat content. In addition, MTP inhibition increases liver transaminases, and these two different aspects may have interacted and worsened the liver condition.[152]

An ongoing study is evaluating the effect of lomitapide treatment on carotid and aortic atherosclerosis in HoFH patients (NCT02399852) and will measure the percent change from baseline in carotid vessel wall area at the 2-year evaluation as well as the percent change from baseline in carotid aortic vessel wall area and thickness at 1- and 5-year intervals (Table 5).

Lomitapide is a weak inhibitor of CYP3A4 and increases the exposure of statin[153]; thus, caution should be used when administered in combination by monitoring the well-known adverse effects associated with statin therapy.

7.18.3.1.5 CETP inhibitors

Cholesteryl ester transfer protein (CETP) is an enzyme mainly involved in the transfer of cholesteryl esters from HDL to LDL and VLDL; this process results in a reduction and remodeling of HDL particles and in an increase of LDL and VLDL levels (Fig. 6). Under pathological conditions, such as atherosclerosis, CETP activity is increased, while CETP deficiency results in increased HDL-C levels. These observations lead to the hypothesis that CETP inhibition might be a powerful tool to increase HDL cholesterol, decrease LDL and VLDL cholesterol, and reduce the development of atherosclerosis.[154]

The first CETP inhibitor (CETPi) developed, torcetrapib (Fig. 7), although very effective in increasing HDL-C levels (+72%), was withdrawn due to the results of the ILLUMINATE trial that reported an increased risk of CV events and death from any cause.[155] This effect was attributed to an off-target effect of torcetrapib independent of CETP inhibition.[155,156]

The Dalcetrapib HDL Evaluation, Atherosclerosis and Reverse Cholesterol Transport program included three surrogate end point trials, dal-VESSEL, dal-PLAQUE, and dal-PLAQUE 2, and the large phase 3 dal-OUTCOMES trial that evaluated the effects of dalcetrapib (Fig. 7) 600 mg daily added to standard statin therapy on mortality and morbidity in more than 15,000 high-risk CHD patients. In May 2012, however, the development of dalcetrapib was stopped based on the interim analysis of the *dal-OUTCOMES* (NCT00658515) trial that reported lack of efficacy in reducing CV events.[157] One possible explanation for this finding may be the moderate effect of dalcetrapib on HDL-C (+20%) and the lack of effect on LDL-C levels.[157]

Three further CETPi's, anacetrapib, evacetrapib (Fig. 7), and TA-8995, have been developed, and the results of the clinical trials are discussed in the succeeding text.

Anacetrapib. Anacetrapib was initially tested (100 mg daily) in patients with CHD or equivalent conditions (peripheral artery disease, cerebrovascular disease, diabetes, or a 10-year Framingham risk score >20%) resulting in the increase of HDL-C levels and in the decrease of LDL-C and apoB levels either as monotherapy or in combination with a statin.[158–160] The effect of LDL-C reduction is due to an increased rate of apoB fractional clearance.[161] The *DEFINE* (*Determining the Efficacy and Tolerability of CETP Inhibition with Anacetrapib*, NCT00685776) trial showed that in patients at high risk of CHD, anacetrapib increased HDL-C by 138.1% and reduced LDL-C by 39.8% compared with placebo[160] (Table 6), although a subsequent reevaluation of lipid parameters using different methods established an LDL-C level reduction closer to 25–35%.[162] Adverse events were comparable between the two groups.[160] The 2-year extension of the DEFINE study showed that treatment with anacetrapib was well tolerated and determined a 39.9% reduction of LDL-C and 153.3% increase of HDL-C compared with placebo.[163] When analyzed in patient subgroups, defined by age, gender, race, or baseline lipid levels or other conditions such as diabetes status or use of other lipid-modifying therapies, these changes in LDL-C and HDL-C levels were comparable across groups.[164] Only age, gender, and race seem to have a slight effect on anacetrapib-mediated effect, with patients <65 years more responsive than those ≥65 years, men more responsive than women, and whites more responsive than blacks.[164] The *REVEAL* (*Randomized Evaluation of the Effects of Anacetrapib through Lipid-modification*, NCT01252953) trial will determine the occurrence of major coronary events

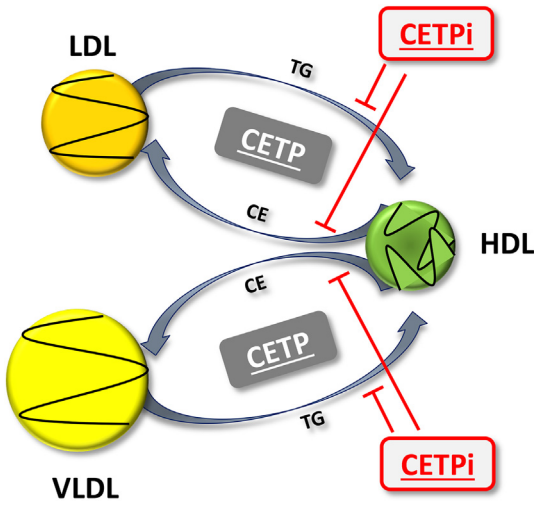

Fig. 6 CETP inhibition. CETP mediates the transfer of cholesteryl ester (CE) from HDL to larger lipoproteins, such as VLDL and LDL, in exchange for triglycerides (TG). This results in the generation of CE-enriched LDL and VLDL and TG-enriched HDL and in the reduction of circulating HDL-C. CETP inhibitors (CETPi's) inhibit the transfer of CE and result in the increase of HDL-C and reduction of LDL-C.

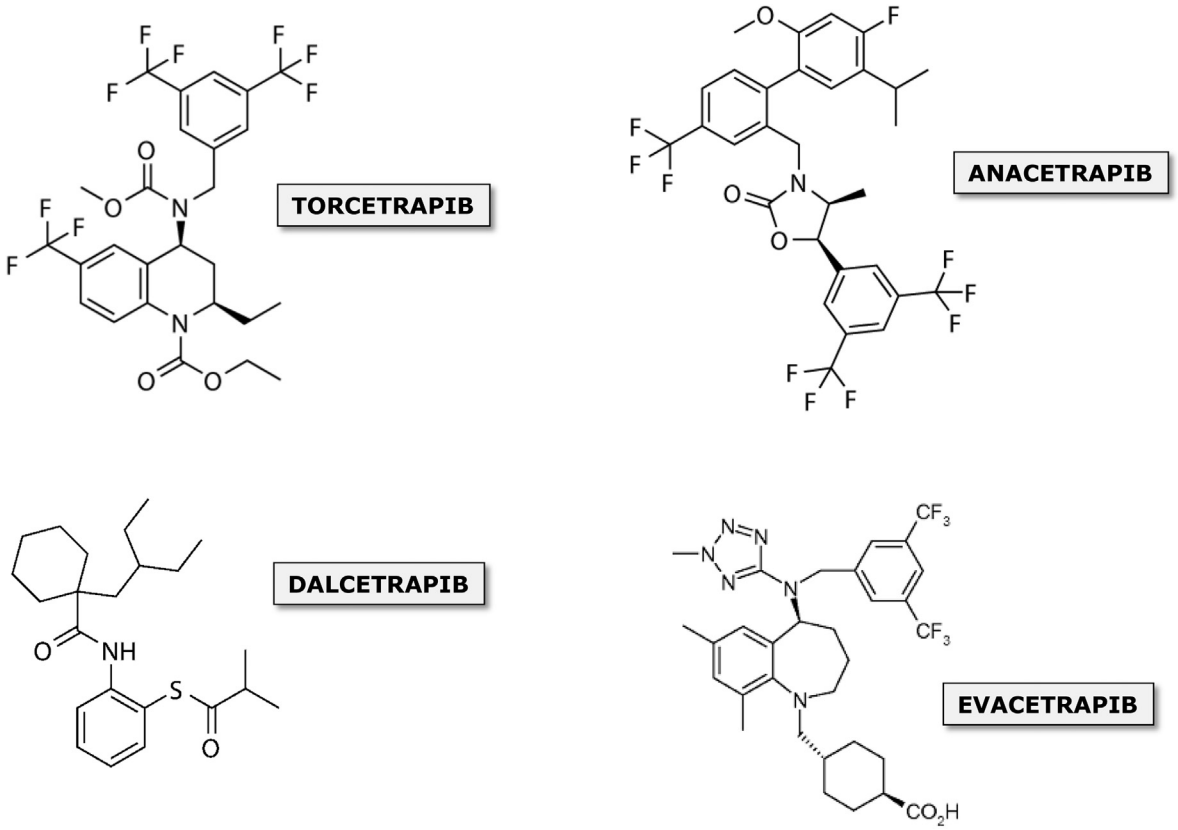

Fig. 7 Structure of CETP inhibitors.

(coronary death, MI, and coronary revascularization procedures) in 30,000 patients with CHD, cerebrovascular atherosclerotic disease, or peripheral artery disease and is estimated to end in 2017.

Anacetrapib has also been tested in patients with HeFH in the phase 3 *REALIZE* study (NCT01524289) that was designed to evaluate the tolerability and efficacy of anacetrapib added to current statin therapy for 52 weeks. This study reported a −39.7% reduction in percent change from baseline in LDL-C versus placebo and a significant increase of HDL-C levels (+105.8% vs. +3.7% with placebo)[165] (Table 6).

Evacetrapib. In a phase 2 study, evacetrapib was effective in reducing LDL-C and increasing HDL-C either as monotherapy (−13.6% to −35.9% and +53.6% to +128.8% from baseline, respectively, vs. +3.9% with placebo) or in combination with statins (Table 6).[166] The *ACCELERATE* (*A Study of Evacetrapib in High-Risk Vascular Disease*, NCT01687998) trial, which enrolled a large population (estimated: 12,000) of patients with diagnosis of high risk of vascular disease to evaluate the time to first occurrence of the composite end point of CV death, MI, stroke, coronary revascularization, or hospitalization for unstable angina in patients administered with evacetrapib or placebo, was stopped early because of futility; in fact, evacetrapib failed to reduce major CV events in these patients when compared with placebo, despite a 130% increase in HDL-C and a 37% decrease in LDL-C.[167]

TA-8995. TA-8995 is a new potent CETPi that demonstrated an almost complete inhibition of CETP, resulting in 96–140% increase of HDL-C and 40–53% reduction of LDL-C in healthy subjects, with no evidence of any off-target effects.[168] The *TULIP* (*TA-8995: Its Use in Patients with Mild Dyslipidemia*, NCT01970215) study evaluated the safety and efficacy of TA-8995 alone or in combination with a statin for 12 weeks.[169] In this trial, TA-8995 reduced LDL-C levels by 45.3% and increased HDL-C by up to 179.1%[169]; when given in combination with a statin, LDL-C levels further decreased (39.8–50.2%)[169] (Table 6). Altogether, we cannot draw a firm conclusion and the results from the REVEAL study will provide a definitive answer.

7.18.3.1.6 ETC-1002

ETC-1002 is a dicarboxylic acid derivative (Fig. 8) that inhibits hepatic adenosine triphosphate citrate lyase (ACL) and activates adenosine monophosphate-activated protein kinase (AMPK), two complementary enzymes involved in the metabolism of lipids and carbohydrates.[170] While ETC-1002-free acid activates liver AMPK, hepatocytes also readily convert the parent compound into ETC-1002-CoA thioester, which has been shown to directly inhibit ACL.[170] The inhibition of ACL results in reduced acetyl coenzyme A (CoA) levels, thus inhibiting both fatty acid and cholesterol synthesis; the activation of AMPK results in the inhibitory phosphorylation of HMG-CoA reductase and acetyl-CoA carboxylase as well as in reduced levels of PEPCK and G6Pase.[170]

Table 6 Effect of new CETP inhibitors

CETP inhibitors	*Subjects*	*Duration*	*LDL-C (percent change from baseline)*	*HDL-C (percent change from baseline)*	*Primary end point for ongoing trials*
Anacetrapib					
DEFINE (NCT00685776)[160]	CHD or CHD risk equivalent Well-controlled LDL-C	76 weeks	−39.8% versus placebo	+138.1% versus placebo	
REVEAL (NCT01252953)	History of MI, cerebrovascular disease, PAD, T2DM with CHD	4 years			Occurrence of major coronary events (coronary death, MI, or coronary revascularization procedure) (completion date: 2017)
REALIZE (NCT01524289)[165]	HeFH treated with optimal dose of statin for at least 6 weeks	52 weeks	−39.7% versus placebo	+102.1% versus placebo	
Evacetrapib					
Nicholls et al.[166]	Low HDL-C or high LDL-C	12 weeks	Monotherapy: −17.6% (30 mg) to −39 8% (500 mg) versus placebo Statin combination: Eva+ Atorva 20, −13.9% versus Atorva 20; Eva+ Simva 40, −11.2% versus Simva 40; Eva+ Rosuva 10, −13.5% versus Rosuva 10	Monotherapy: +56.7% (30 mg) to +131.9% (500 mg) versus placebo Statin combination: Eva+ Atorva 20, +78.5% versus Atorva 20; Eva+ Simva 40, +79.3% versus Simva 40; Eva+ Rosuva 10, +89.5% versus Rosuva 10	
ACCELERATE (NCT01687998)	History of ACS, cerebrovascular disease, PAD, T2DM with stable CAD	4 years			Time to first occurrence of major CV events (CV death, MI, stroke, coronary revascularization, or hospitalization for UA) (completion date: 2016)
TA-8995					
TULIP (NCT01970215)[169]	Mild dyslipidemia	12 weeks	−27.4% to −45.3% (1-10 mg)	+75.8% to +179.0% (1-10 mg)	

CHD, coronary heart disease; *MI*, myocardial infarction; *PAD*, peripheral artery disease; *T2DM*, type 2 diabetes mellitus; *HeFH*, heterozygous familial hypercholesterolemia; *CAD*, coronary artery disease; *ACS*, acute coronary syndrome; *Atorva*, atorvastatin; *Simva*, simvastatin; *Rosuva*, rosuvastatin; Eva, evacetrapib.

ETC-1002 treatment thus results in the reduction of LDL-C and glucose levels. In addition, ETC-1002 possesses anti-inflammatory properties, attenuates leukocyte homing at inflammatory sites, and inhibits adipose tissue inflammation[171] (Fig. 8).

ETC-1002 has been tested in three doses (40, 80, and 120 mg) in 133 subjects with hypercholesterolemia (LDL-C 130–220 mg dL^{-1} and 3.3–5.6 mmol L^{-1}) stratified by baseline normal or elevated TG levels (A Study to Assess the Efficacy and Safety of ETC-1002 in Subjects with Elevated Blood Cholesterol and Either Normal or Elevated Triglycerides, NCT01262638).[172] After 12 weeks of treatment, ETC-1002 significantly reduced LDL-C levels compared with placebo (from −17.9% to −26.6%), independently of baseline TG levels; reduced non-HDL-C, apoB, and LDL particle number in a dose-dependent manner; and was generally safe and well tolerated.[172] A trend in the reduction of high-sensitivity C-reactive protein (hs-CRP) was observed particularly in subjects with higher baseline hs-CRP values.[172] Similar effects were also observed in subjects with type 2 diabetes mellitus and hypercholesterolemia (NCT01607294): ETC-1002 lowered LDL-C levels by 43% and reduced hs-CRP.[173] ETC-1002 has also been tested in hypercholesterolemic patients with a history of statin intolerance (NCT01751984), showing that TC, LDL-C, non-HDL-C, and apoB were significantly decreased by 8-week ETC-1002 treatment compared with placebo (difference from placebo: −18.4%, −28.7%, −20.9%, and −15.3%, respectively).[174] Among the patients in the ETC-1002 treatment arm who were not at LDL-C target 62% reached their goal at the end of the study, while no patients in the placebo arm reached the LDL-C target.[174] Patients treated with ETC-1002 experienced muscle-related adverse events in a percentage similar to those treated with placebo,[174] suggesting that ETC-1002 might be a valuable alternative to statins

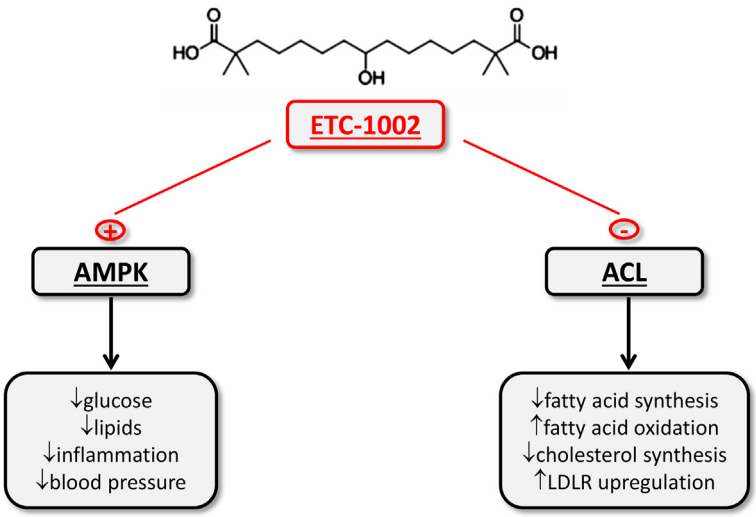

Fig. 8 Dual mechanism of action of ETC-1002. ETC-1002 activates AMP-activated protein kinase (AMPK), thus favorably impacting several metabolic processes, including glucose and lipid metabolism, as well as inflammation. On the other hand, ETC-1002 inhibits ATP citrate lyase (ACL), resulting in the decrease of cholesterol biosynthesis and upregulation of LDLR.

in patients with statin intolerance or as add-on therapy in patients unable to reach LDL-C target despite statin treatment. Future large trials are warranted to confirm these findings.

7.18.3.2 Targeting Plasma TG Levels

High levels of plasma TG are an independent risk factor for atherosclerosis and related CV diseases [175–177]; increased TG levels are usually associated with low HDL-C levels and increased small dense LDL,[178] referred to as atherogenic dyslipidemia.[179] In addition, severe HTG (TG levels $\geq$500 mg dL^{-1} and $\geq$5.65 mmol L^{-1}) significantly increases the risk of acute pancreatitis.[180,181] Thus, several drugs have been developed for the management of HTG, including fibrates, nicotinic acid, and omega-3 polyunsaturated fatty acids. However, new approaches for the management of HTG are now under evaluation.

7.18.3.2.1 Omega-3 free fatty acids

Among the available drugs for the treatment of HTG, there are omega-3 polyunsaturated fatty acids, usually a mixture of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) or EPA alone in their ethyl ester forms. However, to be absorbed in the intestine, the ethyl ester omega-3 polyunsaturated fatty acids need be converted into free acid by pancreatic lipase enzymes.[182] The most recent free fatty acid formulation (Epanova, containing 55% EPA and 20% DHA) is not dependent on pancreatic enzyme activity and is more readily absorbed, even in the condition of a very low fat diet.[182]

The pharmacokinetic parameters of a single dose of omega-3 free fatty acid formulation have been evaluated in comparison with the omega-3 ethyl esters in the *ECLIPSE* (*Epanova® Compared to Lovaza® in a Pharmacokinetic Single-Dose Evaluation*, NCT01208961) study in overweight adults.[183] Under a low fat diet, both EPA and DHA in the free fatty acid form had a higher bioavailability compared with the ethyl ester (ninefold and twofold, respectively).[183] Higher plasma levels of EPA and DHA were found in subjects taking the free fatty acid forms for 14 days compared with subjects taking the ethyl ester form (*ECLIPSE II*), and TG levels were reduced to a greater extent with the free fatty acid form (−21% and −8%, respectively, $P=0.013$),[184] suggesting that omega-3 free fatty acids provide more EPA and DHA under low fat diet conditions, thus resulting in a greater effect on plasma TG levels.

In subjects with severe HTG (TG: $\geq$500 and $\leq$2000 mg dL^{-1}; $\geq$5.65 and $\leq$22.60 mmol L^{-1}) treated with three dosages of 2, 3, and 4 g day^{-1} for 12 weeks in the double-blind, randomized *EVOLVE* (*Epanova for Lowering Very High Triglycerides*, NCT01242527) trial,[185] fasting TG levels were significantly reduced with all doses compared with controls (−25.9%, −25.5%, and −30.9% with 2, 3, and 4 g day^{-1}, respectively, vs. −4.3% of olive oil 4 g day^{-1})[185] (**Table 7**). Despite significant lowering of TC and non-HDL cholesterol, a significant increase of LDL-C was observed (+19.2%, +14.3%, and +19.4% vs. +3.0%) without a concomitant increase of apoB levels,[185] suggesting that the treatment did not increase the number of circulating atherogenic particles. VLDL-C and RLP-C were also significantly reduced in all treatment groups[185] according to the results obtained in studies with the omega-3 ethyl ester formulation[186,187]; also, apolipoprotein C-III (apoC-III) was significantly reduced (−11%, −12%, and −14%, respectively, vs. +1.6%).[185] The analysis of subgroups revealed that high-risk patients with diabetes or baseline TG $\geq$750 mg dL^{-1} ($\geq$8.47 mmol L^{-1}) or the highest tertile of apoC-III or RLP-C may particularly benefit from the treatment with the omega-3 free fatty acid formulation as they reported the most significant reductions in TG and non-HDL-C levels.[188]

The efficacy of free fatty acid formulation of omega-3 as an adjunct to statin therapy and low diet was proved also in high CV risk patients treated with statin and with persistent HTG ($\geq$200 and $<$500 mg dL^{-1}; $\geq$2.26 and $\leq$5.65 mmol L^{-1}) in the *ESPRIT*

Table 7 New TG-lowering drugs

	Subjects	*Duration*	*TG (percent change from baseline)*	*apoC-III (percent change from baseline)*	*Primary end point for ongoing clinical trials*
Omega-3 FFA					
EVOLVE, NCT01242527[185]	HTG	12 weeks	−25.9% (2 g) to −30.9% (4 g)	−10.9% (2 g) to −14.4% (4 g)	
ESPRIT, NCT01408303[189]	Statin-treated patients with residual HTG	6 weeks	−14.6% (2 g) to −20.6% (4 g)		
STRENGTH, NCT02104817[190]	High CVD risk	5 years			Time to the first occurrence of major adverse CV events (completion date: 2019)
ISIS-APOCIIIRx					
Gaudet et al.[200]	FCS	13 weeks	−56% to −86%	−71% to −90%	
NCT01529424[201]	Severe or uncontrolled HTG	13 weeks	Monotherapy: −31.3% (100 mg) to −70.9% (300 mg) Add-on to fibrate: −51% (200 mg) to −64% (300 mg)	Monotherapy: −40.0% (100 mg) to −79.6% (300 mg) Add-on to fibrate: −60.2% (200 mg) to −70.9% (300 mg)	
APPROACH (NCT02211209)	FCS	52 weeks			Percent change in fasting TG from baseline (completion date: 2016)
COMPASS (NCT02300233)	HTG	26 weeks			Percent change in fasting TG from baseline (completion date: 2016)
Pradigastat					
NCT01146522[207]	Hyperlipidemia type I or type V	3 weeks	Fasting TG: −41% (20 mg) to −70% (40 mg) Peak postprandial TG: −38% (20 mg) to −31% (40 mg)		
NCT01514461	FCS	12 weeks	−28.8% (20 mg) −40.9% (40 mg)		

HTG, hypertriglyceridemia; *CVD*, cardiovascular disease; *FCS*, familial chylomicronemia syndrome.

(*Epanova Combined with a Statin in Patients with Hypertriglyceridemia to Reduce Non-HDL Cholesterol*, NCT01408303) trial.[189] TG levels were significantly decreased (−14.6% and −20.6% with 2 and 4 g day^{-1}, respectively) compared with controls (−5.9%, statin + olive oil 4 g day^{-1}) (Table 7); other lipid parameters, including TC, non-HDL-C, and VLDL-C, were significantly improved.[189] Such reductions were higher in patients taking high-potency statins.[189]

The ongoing STRENGTH (*A Long-Term Outcomes Study to Assess Statin Residual Risk Reduction with Epanova in High Cardiovascular Risk Patients with Hypertriglyceridemia*, NCT02104817) trial will evaluate the efficacy of omega-3 free fatty acid formulation in addition to statin therapy in high-risk subjects in the prevention and reduction of major CV events[190] and has as primary outcome the time to the first occurrence of CV death, nonfatal MI, nonfatal stroke, coronary revascularization, or hospitalization for unstable angina (Table 7). The eligible patients that will be in the study for up to 5 years have controlled LDL-C levels ($\leq$100 mg dL^{-1}) but with residual atherogenic dyslipidemia (TG: $\geq$200 and $\leq$500 mg dL^{-1}; HDL-C $<$40 mg dL^{-1} for men and $<$45 mg dL^{-1} for women).

Overall, the free fatty acid formulation of EPA and DHA is well tolerated, and the most common adverse effects are mild to moderate gastrointestinal disorders[183–185,189]; in addition, its higher bioavailability may allow treatment with lower doses, thus likely increasing the drug compliance. Whether the lipid-lowering effect of free fatty acid EPA and DHA can translate into a CV benefit remains to be addressed.

7.18.3.2.2 Alipogene tiparvovec

Lipoprotein lipase deficiency (LPLD) is a rare autosomal recessive disease caused by loss-of-function mutations of *LPL* gene and is characterized by hyperchylomicronemia, severe HTG, and high risk of diabetes mellitus and recurrent, acute pancreatitis.[191] Alipogene tiparvovec is the first adeno-associated virus-mediated gene therapy approved for the treatment of LPLD[192]; in fact, the intramuscular administration of alipogene tiparvovec delivers a natural gain-of-function variant of LPL that results in a significant improvement of TG-rich lipoprotein characteristics and relevant reduction in the incidence of pancreatitis.[191] In the initial 12-week study performed in LPLD patients with baseline TG levels $>$14 mmol L^{-1}, the injection of a single alipogene tiparvovec dose induced local LPL expression and significant but transient reduction of TG levels (27–41%).[193] In an open-label clinical trial,

intramuscular administration of alipogene tiparvovec resulted in a significant improvement of postprandial chylomicron metabolism in LPLD patients, without changes in postprandial nonesterified fatty acids.[194] Overall, there was a reduction in the risk of pancreatitis after up to 6 years follow-up after gene therapy.[191] Alipogene tiparvovec was well tolerated; however, LPLD being a rare disease, it is very difficult to undertake clinical trials to define the safety and efficacy of this therapeutic approach.

7.18.3.2.3 ISIS-APOCIIIRx

apoC-III is a glycoprotein mainly associated with VLDL and chylomicron and, to a lesser extent, with HDL; it plays a critical role in the metabolism of TG-rich lipoproteins as it acts as potent inhibitor of lipoprotein lipase (and, when present at high concentrations, of hepatic lipase) but is also involved in the hepatic VLDL assembly and secretion.[195] apoC-III plasma levels are independently associated with the progression of CV disease[195]; loss-of-function variants of *APOC3* gene are associated with low TG levels and reduced risk of ischemic CV disease.[196,197] Several drugs used for the treatment of HTG also reduce apoC-III levels, including fibrates, peroxisome proliferator-activated receptor agonists, and omega-3 polyunsaturated fatty acids.[195] However, these drugs may decrease apoC-III levels by only 10–30%, while larger apoC-III reductions seem to be required to observe a clinical benefit similar to that reported in subjects carrying genetic mutations in *APOC3*.[196,197]

ISIS-APOCIIIRx is a second-generation 2′-*O*-(2-methoxyethyl)-modified ASO that inhibits the hepatic synthesis of apoC-III (Fig. 4). In healthy human volunteers without HTG, ISIS-APOCIIIRx induced a dose-dependent and prolonged reduction of apoC-III and TG levels.[198] In the multiple-dose phase, healthy subjects were treated for 22 days with six total doses of 50, 100, 200, or 400 mg ISIS-APOCIIIRx, showing median percentage reductions of apoC-III levels from baseline to 19.7%, 17.3%, 70.5%, and >77%, respectively, associated with dose-dependent reductions of TG levels (from −19.5% to 43.8%).[198]

ISIS-APOCIIIRx was also tested in three patients with familial chylomicronemia syndrome (FCS), a rare autosomal recessive disease caused by mutations in the gene encoding LPL or genes encoding proteins involved in LPL function, and characterized by high levels of plasma chylomicrons and severe HTG, with a high risk of recurrent acute pancreatitis.[199] After a 13-week treatment, ISIS-APOCIIIRx significantly reduced apoC-III (71–90%) and TG levels (56–86%)[200] (Table 7). Reductions of TG levels in chylomicrons, apoB-48 levels, and non-HDL-C were also reported; the reduction of non-HDL-C was due to the reduction of chylomicron/VLDL cholesterol, while LDL-C levels that were extremely low at baseline (13–17 mg dL^{-1}) resulted unchanged or increased (up to 35.5 mg dL^{-1}).[200]

In the phase 2 randomized trial, ISIS-APOCIIIRx was given once weekly for 13 weeks to patients with severe or uncontrolled HTG, having fasting TG between 350 and 2000 mg dL^{-1} (4.0–22.6 mmol L^{-1}), and to patients on stable fibrate therapy having fasting TG levels between 225 and 2000 mg dL^{-1} (2.5–22.6 mmol L^{-1}) (NCT01529424). Both groups showed significant reductions of plasma apoC-III and TG levels either when the drug was administered as monotherapy or when it was administered as add-on to stable fibrate therapy[201] (Table 7). The large decrease of TG resulted in a dose-dependent increase of LDL-C levels following the treatment with ISIS-APOCIIIRx, associated with increases in apoB levels and LDL particle size[201]; despite this, non-HDL-C was unchanged.[201] This effect on LDL-C levels may be due to the increased conversion of VLDL to LDL determined by the increased activity of LPL, but other mechanisms may contribute as well. The clinical significance of this increase requires further investigation.

Two ongoing phase 3 trials, the *APPROACH* (*The APPROACH Study: A Study of ISIS-APOCIIIRx in Patients with Familial Chylomicronemia Syndrome*, NCT02211209) and *COMPASS* (*The COMPASS Study: A Study of ISIS-APOCIIIRx in Patients with Hypertriglyceridemia*, NCT02300233) trials, will evaluate the efficacy and safety of ISIS-APOCIIIRx. The APPROACH trial will recruit patients with a history of chylomicronemia and a diagnosis of FCS and fasting TG levels ≥750 mg dL^{-1} (8.4 mmol L^{-1}) who will be treated with 300 mg ISIS-APOCIIIRx administered subcutaneously once weekly for 52 weeks versus placebo. The COMPASS trial will recruit HTG patients with fasting TG ≥500 mg dL^{-1} (≥5.7 mmol L^{-1}) who will be administered 300 mg ISIS-APOCIIIRx versus placebo subcutaneously once weekly for 26 weeks. Both trials have as primary outcome the percent change in fasting TG from baseline.

7.18.3.2.4 Diacylglycerol O-acyltransferase inhibitors

TGs are synthesized in enterocytes and hepatocytes and then assembled into lipoproteins and secreted to transport dietary and endogenous fatty acids. TGs are essential for several functions, among which energy storage and membrane composition represent the most important. However, excess TGs are associated with obesity, insulin resistance, nonalcoholic steatohepatitis, and CV disease.[202]

Diacylglycerol *O*-acyltransferase (DGAT) enzymes catalyze the formation of an ester linkage between a fatty acyl-CoA and diacylglycerol. The two enzymes DGAT1 and DGAT2, encoded by two different genes not sharing significant sequence homology, have a different subcellular localization and are differently regulated, suggesting that they likely participate in different pathways of TG synthesis and thus have distinct physiological functions.[202] DGAT2 seems thus to be involved in the incorporation of endogenously synthesized monounsaturated fatty acids into TG, while DGAT1 appears to be involved in the esterification of exogenous fatty acids taken up by cells.[202]

Mice lacking DGAT1, although capable of synthesizing TG (indicating the existence of alternative mechanisms for TG synthesis), have reduced body TG content and are resistant to diet-induced obesity,[203] while mice lacking DGAT2 have severe lipopenia and die soon after birth [204]; this suggests that DGAT1 and DGAT2 play different roles and that DGAT2 plays an essential role in the synthesis of TG in mammals and is required for survival, while DGAT1 is not. Based on these observations, it has been hypothesized that the pharmacological inhibition of DGAT1 could be an attractive way to control HTG. Several preclinical models have shown that treatment with DGAT1 inhibitors inhibits postprandial plasma TG excursion after a lipid challenge and, when administered chronically, metabolic parameters are improved.[205]

Pradigastat in healthy volunteers suppressed postprandial TG in a dose-dependent manner and reduced postprandial chylomicron numbers (as determined by the apoB-48 reduced levels).[206] The DGAT1 inhibitor pradigastat has been tested in six patients with FCS (NCT01146522), who underwent three consecutive 3-week treatment periods (20, 40, and 10 mg, respectively) separated by 4-week washout periods.[207] Pradigastat 20 and 40 mg reduced plasma TG by 41% and 70%, respectively, in FCS patients, while the lowest dose was ineffective (Table 7). More specifically, it mainly reduced the size and TG content of secreted chylomicrons[207] that in FCS transport almost all plasma TG (contrarily to healthy subjects that present their fasting TG almost completely in VLDL, while postprandial TG are equally shared between VLDL and chylomicrons). In a phase 3 study (NCT01514461), a −28.8% with 20 mg and −40.9% with 40 mg pradigastat versus placebo was reported after a 12-week treatment in FCS patients (Table 7). When tested in obese patients with type 2 diabetes mellitus in a 2–20 mg dose range (NCT00901979), pradigastat had beneficial effects on several metabolic parameters, including TG, LDL-C, TC, and body weight.[208]

7.18.3.3 Conclusions

Several novel therapeutic approaches have been investigated in the last few years with the aim of reducing plasma cholesterol and TG levels. For cholesterol, with the most potent statins, we have reached a highly effective inhibition of cholesterol biosynthesis in the liver; therefore, from a pharmacological perspective, the development of novel strategies has been focused on different mechanisms of action, including the inhibition of cholesterol absorption in the intestine (ezetimibe), the inhibition of lipoprotein synthesis (lomitapide and mipomersen), and the improvement of lipoprotein catabolism (PCSK9 inhibitors). In FH patients, clinical trials of these new compounds were proved to be successful in decreasing plasma cholesterol levels and reducing the burden of CV diseases.

See also: 8.11. Case Histories: Anacetrapib. 8.13. Fragment-Based Discovery of AZD2716: A Novel, Potent Secreted Phospholipase A_2 ($sPLA_2$) Inhibitor for the Treatment of Coronary Artery Disease.

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