Management of hypercholesterolemia, appropriateness of therapeutic approaches and new drugs in patients with high cardiovascular risk

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ABSTRACT

Hypercholesterolemia is a major risk factor for cardiovascular disease (CVD). Lowering low-density lipoproteins-cholesterol (LDL-C) has been shown to decrease the risk of CVD and of all-cause mortality. For appropriate management, estimation of each individual's total cardiovascular risk is critical, as patients should receive treatment according to their cardiovascular risk category as well as their LDL-C level. However, available data indicate that a large proportion of patients fail to achieve lipid goals despite treatment, and a significant percentage of patients are not able to tolerate statin treatment. Researchers have therefore focused considerable attention on the development of novel LDL-C-lowering agents that act via different mechanisms. Among the most recent advances in clinical development are the proprotein convertase subtilisin/kexin 9 antibody inhibitors, including alirocumab and evolocumab, which appear particularly promising, with clinical trial data indicating these agents to be both well tolerated and highly efficacious in lowering LDL-C.

Introduction

Hypercholesterolemia and elevated plasmatic levels of low-density lipoproteins-cholesterol (LDL-C) - are major risk factors for cardiovascular disease (CVD) - the leading cause of death worldwide.[1] While hypercholesterolemia is asymptomatic, it can lead to atherosclerosis, stenosis of blood vessels and eventual clinical vascular disease. Importantly, there is a strong graded association between elevated total plasma cholesterol and LDL-C levels and increased cardiovascular risk in those with and without existing CVD.[1]

Hypercholesterolemia can be primary, *i.e.* due to an inherited disease [familial hypercholesterolemia (FH)] with several genes contributing to increased LDL-C levels,[2] or it can be secondary to other diseases, such as obesity, diabetes, alcohol abuse, unbalanced nutrition, Cushing's syndrome, hepatic and renal disease,[3] and drug related, including corticosteroids, isotretinoin and etretinate, and cyclosporine.[1]

Familial (hyperlipoproteinemia type IIa) hypercholesterolemia comprises heterozygous FH (HeFH), which has been attributed to a heterozygous variant in one of three genes (*LDLR*, *APOB*, *PCSK9*), accounting for 70-95% of FH, and homozygous FH (HoFH),[4] caused by either two mutations in one of these known genes or one mutation in each of two different genes.

Lowering LDL-C has been shown to decrease the risk of CVD and of all-cause mortality.[1] However, while the evidence pointing to the importance of reducing LDL-C levels to reduce cardiovascular morbidity and mortality is unequivocal, a high proportion of patients are statin-intolerant[5] and/or refractory. In patients who are inadequately treated, or who respond poorly to treatment, there is increased cardiovascular risk and suboptimal CVD prevention.[1] Here we review current management of hypercholesterolemia, the appropriateness of existing therapeutic approaches and the need for novel drugs in patients with high cardiovascular risk.

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Methods of research

This narrative review comprised an automated literature search strategy and manual selection using PubMed, with no date or other limits. Search terms used were '*hypercholesterolaemia/-emia*', '*treatment/therapy/drug'*, '*high cardiovascular/cardiovascular risk*', with further manual searches performed to find papers relating to treatments for patients who do not respond adequately to statin therapy or do not achieve LDL-C targets on statins. Specific drug searches were performed using these general terms AND '*alirocumab'*, '*evolocumab'*, '*lomitapide'* OR '*mipomersen'*, with manual searches performed to find relevant treatment guidelines. Other papers were provided by the authors from their own libraries or were selected from the bibliographies of articles found in the automated search.

Cardiovascular risk

Estimation of a patient's total cardiovascular risk is critical for the appropriate management of each individual patient.[6] There are certain factors known to place patients at high risk of cardiovascular events, including very high LDL-C.[1] Risk assessment should include assessment of traditional atherosclerotic risk factors: age, sex, total and high-density lipoproteins-cholesterol (HDL-C), systolic blood pressure, use of antihypertensive therapy, diabetes, and current smoking status,[7] and a risk estimation, such as the Systematic Coronary Risk Evaluation Project (SCORE) system, should be used. The SCORE system provides an assessment of 10-year risk of a first fatal atherosclerotic event, including heart attack, stroke, aneurysm of the aorta, and sudden cardiac death.[1,8] The method of assessing total risk allows for risk reduction strategies from multiple angles, if one risk factor cannot be adequately addressed, risk can still be reduced by focusing on other factors.[1]

Standard management

Patients should receive treatment according to their cardiovascular risk category and LDL-C level:[9] the first priority should be LDL-C lowering with statins with or without other lipid-modifying therapies (LMTs), to lipid targets defined according to the SCORE risk categories. However, there should also be emphasis on lifestyle modifications. Modulation of absolute risk with a combination of lifestyle changes and control of LDL-C hypercholesterolemia, especially in those with diabetes/metabolic syndrome, is of the utmost importance. The most significant reduction in cardiovascular risk is achieved through LDL-C reduction with statin therapy, and while other LMTs (fibrate, niacin, or ezetimibe) are adjunctive therapies, clinical trials data do not show the same degree of cardiovascular risk reduction, compared with statins, when used as monotherapy.[9]

For statin-refractory patients, options for adjunctive pharmacotherapy include: ezetimibe, a cholesterol absorption inhibitor, used in combination with statins; bile acid sequestrants or resins, *e.g.* colesevelam, which block reabsorption of lipids; peroxisome proliferator-activated receptor alpha agonists or fibrates, *e.g.* fenofibrate, which act mainly to increase HDL-C and lower triglycerides (TG); niacin/nicotinic acids, which mainly increase HDL-C and lower TG but also lower lipoprotein A, a highly atherogenic form of LDL-C; apolipoprotein B (apo B) inhibitors, *e.g.* mipomersen (adjunctive therapy in HoFH); microsomal triglyceride transfer protein (MTP) inhibitor lomitapide (FH) and LDL apheresis for severe hypercholesterolaemia.[10]

Guidelines and treatment algorithms

The UK National Institute for Health and Care Excellence (NICE) lipid modification guidelines for the primary and secondary prevention of CVD recommend that benefits of lifestyle modification are discussed and management of modifiable CVD risk factors is optimised.[11] Regarding treatment for the prevention of CVD, the NICE guidelines recommend atorvastatin 20 mg for primary prevention in those with a 10% or greater 10-year risk of developing CVD, and atorvastatin 80 mg in people with CVD; in those unable to tolerate high-intensity statins, treatment should be with the maximum tolerated dose. People with primary hypercholesterolemia should be considered for ezetimibe monotherapy if statins are not tolerated or contraindicated, or ezetimibe in combination with a statin when cholesterol targets are not able to be met with statin therapy alone.[11] Bile acid sequestrants and nicotinic acid should not be offered for primary or secondary prevention of CVD, alone or in combination with a statin.

Similarly, the European Society of Cardiology (ESC) guidelines recommend statins as first choice lipid-lowering therapy (LLT), and that these should be used at highest tolerated dose to reach target LDL-C levels before considering combination therapy. The ESC guidelines note that combinations of a statin with ezetimibe or, in contrast to the NICE guidelines, a bile acid sequestrant, may be used for greater reduction of LDL-C than can be achieved with either drug alone.[1]

ESC/European Atherosclerosis Society (EAS) guidelines on dyslipidemia treatment maintain that LDL-C remains the primary target of therapy in most strategies of dyslipidemia management.[1] These

guidelines recommend modulating the intensity of the preventive intervention according to total CV risk, suggesting target LDL-C levels of <100 mg/dL in high risk patients, <70 mg/dL in very high risk patients, with <115 mg/dL suggested for patients at moderate risk. Choice of statin therapy should be that expected to produce the LDL-C reduction necessary for a given patient, with up-titration of the dose to reach the target. These guidelines recommend drug combinations with statins and bile acid sequestrants, ezetimibe or nicotinic acid if target levels are not reached.[9]

Reasons for unmet need

Despite the availability of numerous therapies, many patients with high cardiovascular risk do not achieve the LDL-C targets required to minimize their risk.[1,7] This is due in part to a lack of efficacy or intolerance to statins and other treatments, as well as difficulties in reaching therapeutic targets. However, many patients fail to achieve LDL-C targets because of non-adherence to the drug regimen, reasons for which include the asymptomatic nature of hypercholesterolemia and low perceived risk among patients who have no personal history of CVD. Another major factor is undertreatment or inadequate treatment.[12-14]

Novel therapies

Profile of an ideal lipid-modifying therapy for patients with high cardiovascular risk

An ideal LMT for patients at high cardiovascular risk should be effective and well tolerated, while being convenient and easy to administer, and able to be used in all patient subsets, including those with renal or hepatic impairment and in elderly patients. An ideal agent would also be free from any major drug-drug interactions and would be able to be used in combination with statins in those failing to achieve LDL-C targets with statin therapy or as monotherapy in statin-intolerant patients.[15] Among the most recent advances in clinical development are the proprotein convertase subtilisin/kexin 9 antibody (PCSK9) inhibitors.[16]

Proprotein convertase subtilisin/kexin 9 antibody inhibitors

Alirocumab

Alirocumab is a monoclonal antibody against PCSK9 currently approved in the US and EU. In the EU, alirocumab is indicated in adults with primary hypercholesterolemia or mixed dyslipidemia, in combination with a statin or statin with other LLT in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin.[17] Alirocumab blocks the PCSK9 interactions with surface LDL receptor (LDLR)[18] and has been shown to have a statin-enhancing effect.[19]

Three double-blind, placebo-controlled, phase II, randomized controlled trials of alirocumab of 8- or 12-week duration in patients with hypercholesterolemia on background LMT confirmed the promising results in phase I studies. In a study of 183 patients with elevated LDL-C levels on stable atorvastatin, alirocumab was associated with reductions in LDL-C ranging from 40% to 72% for every 2-week (Q2W) dosing and 43% to 48% with every 4-week (Q4W) dosing.[20] Alirocumab was generally well tolerated, but there was one rare event of leukocytoclastic vasculitis reported in this study and thought to be related to study drug administration by investigators.[20]

Alirocumab was also investigated at phase II in patients with HeFH receiving stable statin treatment with or without ezetimibe.[21] In this 77-patient randomized, multicenter, placebo-controlled study, reductions in LDL-C levels after 12-week treatment were 29%, 32%, and 43% in the alirocumab 150 mg, 200 mg, and 300 mg Q4W groups, respectively, and 68% in the alirocumab 150 mg Q2W group (compared with 11% in placebo recipients).[21] In a subsequent phase II study, alirocumab was investigated in patients with elevated LDL-C levels after receiving atorvastatin 10 mg for ≥7 weeks.[22] Significant reductions in LDL-C were seen with alirocumab 150 mg Q2W plus atorvastatin 10 mg/day and atorvastatin 80 mg/day, compared with atorvastatin 80 mg/day plus placebo.[22]

The phase III ODYSSEY clinical trial program currently comprises 15 studies across a range of patient groups and clinical settings and involves more than 23,500 planned patients (Table 1).[17,23-35] The primary results for the following ODYSSEY studies have been fully published: ODYSSEY COMBO I[23] and II,[24] ODYSSEY MONO,[25] ODYSSEY FH I and II,[26] ODYSSEY OPTIONS I[27] and II,[28] ODYSSEY LONG TERM,[17] ODYSSEY HIGH FH,[29] ODYSSEY ALTERNATIVE,[30] ODYSSEY CHOICE I[31] and II,[32] ODYSSEY ESCAPE,[33] ODYSSEY JAPAN[34] and ODYSSEY KT.[35]

The ODYSSEY FH I and II,[26] ODYSSEY HIGH FH[29] and ODYSSEY ESCAPE[33] studies were multicenter, multinational, randomized, double-blind, placebo-controlled studies conducted in patients with HeFH. The ODYSSEY FH studies assessed efficacy and safety of alirocumab in patients with HeFH who, despite maximally-tolerated statin dose, with or without other LLT, continue to have suboptimal LDL-C levels. In the ODYSSEY FH I and II studies, 735 such patients were randomized to SC alirocumab 75 mg Q2W or placebo with the alirocumab dose

Table 1. Summary of alirocumab clinical trials: change in low-density lipoproteins-cholesterol from baseline to week 24.

Study	Patient population	Entry statin	LDL-C change from baseline*				
			Alirocumab	Placebo	Ezetimibe 10 mg/day	Double statin dose	Switch to rosuvastatin (40 mg/day)
ODYSSEY FH I[26]	HeFH	NR	(n=323) –49%	(n=163) 9%	-	-	-
ODYSSEY FH II[26]	HeFH	NR	(n=167) –49%	(n=82) 3%	-	-	-
ODYSSEY COMBO I[23]	Hypercholesterolemia in high CV risk population	NR	(n=205) –48%	(n=106) –2%	-	-	-
ODYSSEY COMBO II[24]	Hypercholesterolemia in high CV risk population	Atorvastatin, rosuvastatin, simvastatin	(n=467) –51%	(n=240) –21%	-	-	-
ODYSSEY MONO[25]	Hypercholesterolemia not on other LLT	NR	(n=52) –47%	-	(n=51) –16%	-	-
ODYSSEY OPTIONS I[27]	HeFH or uncontrolled primary hypercholesterolemia at high CV risk	Atorvastatin 20 mg Atorvastatin 40 mg	(n=55) –44% (n=46) –54%	- -	(n=53) –21% (n=46) –23%	(n=53) –5% (n=47) –5%	- (n=45) –21%
ODYSSEY OPTIONS II[28]	HeFH or uncontrolled primary hypercholesterolemia at high CV risk	Rosuvastatin 10 mg Rosuvastatin 20 mg	(n=48) –51% (n=53) –36%	- -	(n=47) –14% (n=50) –11%	(n=48) –16% (n=52) –16%	-
ODYSSEY LONG TERM[17]	HeFH and hypercholesterolemia in high CV risk population	NR	(n=1530) –61%	(n=780) 1%	-	-	-
ODYSSEY HIGH FH[29]	HeFH	NR	(n=71) –46%	(n=35) –7%	-	-	-
ODYSSEY ALTERNATIVE[30]	Statin-intolerant patients with primary hypercholesterolemia (familial and non-familial)	NR NR	(n=126) –45% (n=183) –52.7%	(n=122) –15% (n=73) –0.3%	- -	- -	- -
ODYSSEY CHOICE I[31]	Hypercholesterolemia in moderate-to-very -high CV risk population	Rosuvastatin (20-40 mg), atorvastatin (40-80 mg) or simvastatin (80 mg)	(n=390) –58.8%	(n=157) –0.1%	-	-	-
ODYSSEY CHOICE II[32]	Hypercholesterolemia, not receiving a statin	NR	(n=116) –53.5%	(n=58) 4.7%	-	-	-
ODYSSEY ESCAPE[33]	HeFH undergoing regular (weekly or Q2W) lipoprotein apheresis	NR	(n=41) –53.7%	(n=21) 1.6%	-	-	-
ODYSSEY JAPAN[34]	HeFH, non-FH with high CV risk or category III classification, in Japan	NR	(n=144) –62.5%	(n=72) 1.6%	-	-	-
ODYSSEY KT[35]	Hypercholesterolemia, with high CV risk, taking maximum tolerated statin dose, from South Korea or Taiwan	Atorvastatin rosuvastatin or simvastatin	(n=97) –57.1%	(n=102) 6.3%	-	-	-

*Least squares mean change from baseline. LDL-C, low-density lipoproteins-cholesterol; HeFH, heterozygous familial hypercholesterolemia; CV, cardiovascular; LLT, lipid-lowering therapy; Q2W, every 2 weeks; Q4W, every 4 weeks.

increased to 150 mg Q2W if LDL-C remained >70 mg/dL after 8 weeks. Alirocumab significantly reduced LDL-C from baseline to week 24 compared with placebo and safety and tolerability were generally comparable in the two groups.[26]

ODYSSEY HIGH-FH randomized a total of 107 HeFH patients with LDL-C levels ≥160 mg/dL despite maximally tolerated treatment with statins and other LLT to alirocumab 150 mg Q2W or placebo.[29] Significant reductions in LDL-C from baseline to week 24 were observed with alirocumab, compared with placebo. Alirocumab was generally well tolerated and total adverse events were comparable with the placebo group.

ODYSSEY ESCAPE evaluated the effect of alirocumab on the frequency of apheresis treatments in patients with HeFH.[33] In this double-blind, randomized trial, patients receiving alirocumab 150 mg had a significant change in pre-apheresis LDL-C, compared with those receiving placebo.

The ODYSSEY ALTERNATIVE study investigated the role of alirocumab, compared with ezetimibe in patients with primary hypercholesterolemia and moderate, high, or very high CV risk, intolerant to statins.[30] After a 4-week placebo run-in phase, 314 patients were randomized to SC alirocumab 75 or 150 mg Q2W, ezetimibe 10 mg/day, or atorvastatin 20 mg/day for 24 weeks. Alirocumab resulted in a significant reduction from baseline than ezetimibe; adverse events were similar between groups.

ODYSSEY COMBO I and II were designed to evaluate the long-term efficacy and safety of alirocumab as add-on therapy to stable, maximally tolerated, daily statin therapy in patients with hypercholesterolemia at high cardiovascular risk.[23,24] In COMBO I, 316 patients were randomized to alirocumab 75 mg Q2W (with the potential to increase to 150 mg Q2W) or placebo.[23] Alirocumab was associated with significant reductions in LDL-C; treatment-emergent adverse events were generally comparable between the two groups. In the 104-week COMBO II study, patients were randomized to alirocumab 75 mg Q2W or ezetimibe 10 mg/day on a background of stable statin therapy.[24] At 24 weeks, there was a LS mean difference in reduction in LDL-C from baseline between alirocumab and ezetimibe of –30%. In COMBO II, the LDL-C lowering ability of alirocumab was maintained over 2 years of treatment, with a significant reduction in LDL-C at 2 years with alirocumab, compared with ezetimibe.[36] Alirocumab was generally well tolerated, with no evidence of an excess of treatment-emergent adverse events.[24,36]

In ODYSSEY MONO, alirocumab monotherapy was investigated in 103 patients with LDL-C 100-190 mg/dL and an estimated 10-year fatal CVD risk SCORE ≥1% and <5%. Patients were randomly assigned to alirocumab 75 mg Q2W or ezetimibe 10 mg/day.[25] After 24 weeks, the alirocumab group showed a significant reduction in LDL-C; adverse events were similar between the two groups.

ODYSSEY OPTIONS I and II, investigated alirocumab as add-on to statin therapy (atorvastatin 20 or 40 mg/day in OPTIONS I;[27] rosuvastatin 10 or 20 mg/day in OPTIONS II[28]) compared with intensification of statin therapy, switching statin therapy or the addition of ezetimibe in patients at high cardiovascular risk and elevated LDL-C levels.[27,28] A total of 660 patients were randomized and, at week 24, alirocumab significantly reduced LDL-C levels in patients receiving atorvastatin 20 or 40 mg at baseline or rosuvastatin 10 mg at baseline.

ODYSSEY CHOICE I and II evaluated the effect of alirocumab in patients with hypercholesterolemia receiving LLTs with either a maximum statin dose or no statin (CHOICE I)[31] or with inadequately controlled hypercholesterolemia, not on statins, receiving treatment with fenofibrate, ezetimibe, or diet (CHOICE II).[32] In ODYSSEY CHOICE I, LDL-C was significantly reduced from baseline to week 24 in patients receiving alirocumab 300mg every 4 weeks (Q4W) compared with placebo.[31] In CHOICE II patients who received alirocumab (150 mg Q4W or 75 mg Q2W) had a –51.7% and –53.5% change in mean LDL-C from baseline to week 24, compared with an increase of 4.7% in the placebo group.[32] Treatment-emergent adverse events were similar between treatment and placebo groups in both studies and ranged from 61.1-75.0% in the placebo group of both studies, 71.5-78.1% in alirocumab 300 mg Q4W (CHOICE I),[31] 77.6% in alirocumab 150 mg Q4W and 73.0% in alirocumab 75 mg Q2W (CHOICE II).[32]

ODYSSEY LONG TERM was a 78-week trial comparing alirocumab (150 mg Q2W) with placebo in 2341 patients at high cardiovascular risk receiving treatment with maximally tolerated statin doses with or without other LLT.[17] All patients had elevated LDL-C (≥70 mg/dL) despite LLT for ≥4 weeks prior to screening. Patients were randomized to alirocumab 150 mg or placebo Q2W for 78 weeks. At week 24, the mean change from baseline in LDL-C between alirocumab and placebo was –62%, and the treatment effect remained consistent up to 78 weeks; the percentage of patients with any adverse event was similar in the two study groups. In a post hoc analysis, the rate of major adverse cardiovascular events was lower with alirocumab than with placebo (1.7% *vs* 3.3%; hazard ratio: 0.52; 95% confidence interval: 0.31-0.90; P=0.02).[17]

The role of alirocumab in Asian patients was investigated in ODYSSEY JAPAN and ODYSSEY KT. ODYSSEY JAPAN was conducted in 216 Japanese patients with HeFH or patients with

hypercholesterolemia at high cardiovascular risk and found that alirocumab significantly reduced LDL-C, compared with placebo. The reduction was sustained over 52 weeks.[34] ODYSSEY KT, which investigated the efficacy and safety of alirocumab in patients from South Korea and Taiwan, found that LDL-C was significantly reduced after 24 weeks in patients receiving alirocumab, compared with placebo.[35] In both studies, treatment-emergent adverse events were comparable between both groups.[34,35]

The role of alirocumab in reducing cardiovascular morbidity and mortality in patients with recent acute coronary syndrome and elevated levels of LDL-C despite therapy with intensive (or maximally tolerated doses) of atorvastatin or rosuvastatin was further investigated in the phase III placebo-controlled ODYSSEY OUTCOMES trial.[37] Patients were randomized to receive subcutaneous alirocumab 75-150 mg Q2W or placebo, with cardiovascular events as the primary efficacy endpoint. Due to the high pricing of alirocumab, patients with HeFH and those with atherosclerotic CVD who have significantly elevated LDL-C on maximally tolerated statin plus ezetimibe were prioritized for treatment. Based on subgroup analysis of ODYSSEY OUTCOMES trial, the cost-benefit ratio is likely to favor patients with an event associated with acute coronary syndrome within the preceding 12 months.[38,39]

Evolocumab

Evolocumab is a PCSK9 inhibitor, which is approved in Europe for the treatment of adults with primary hypercholesterolemia (HeFH and non-familial), mixed dyslipidemias and HoFH in combination with other lipid-lowering therapies and in the US for patients with HeFH, HoFH or clinical atherosclerotic CVD also receiving the maximally-tolerated statin therapy. Evolocumab has been evaluated in several phase III studies in various patient subsets (Table 2).[40-49] In the phase III DESCARTES randomized controlled 52-week trial, evolocumab added to diet, or to atorvastatin with or without ezetimibe significantly reduced LDL-C levels in patients with a range of cardiovascular risk.[40] Similarly, in the MENDEL-2 trial conducted in a large population of patients with primary hypercholesterolemia not confounded by statin use or a history of statin intolerance, evolocumab reduced LDL-C from baseline.[41] The 12-week GAUSS-2 phase III study compared evolocumab 140 mg Q2W or 420 mg Q4W with daily oral ezetimibe 10 mg in 307 statin-intolerant hypercholesterolemic patients and also demonstrated significant reductions in LDL-C from baseline for evolocumab compared with ezetimibe.[42] In the TESLA phase III study, evolocumab was investigated in patients with HoFH

Table 2. Summary of evolocumab clinical trials: change in low-density lipoproteins-cholesterol from baseline to week 12.

Study	Patient population	LDL-C change from baseline*					
		Evolocumab		Placebo		Ezetimibe	
		140 Q2W	420 Q4W	Q2W	Q4W	Q2W	Q4W
MENDEL-2[41]	Patients not receiving drug therapy	(n=153) –57%	(n=153) –56%	(n=76) –0.1%	(n=78) –3.2%	(n=77) –18%	(n=77) –19%
GAUSS-2[42]	Hypercholesterolemia intolerant to statins	(n=103) –56%	(n=102) –55%	-	-	(n=51) –19%	(n=51) –17%
TESLA Part B[43]	HoFH not on apheresis	-	(n=33)	-	(n=16)	-	-
			–23%		8%		
RUTHERFORD-2[44]	HeFH	(n=110) –61%	(n=110) –56%	(n=54) –2%	(n=55) 5.5%	-	-
LAPLACE-2[45 °]	Hypercholesterolemia on background statins	–59% to –66%	–62% to –65%	3% to 13%	0% to 10%	–17% to –24%	–19% to –21%
DESCARTES[40] (week 52)	Hyperlipidemia and mixed dyslipidemia	-	(n=599) –57%	-	(n=302) 7%	-	-
GLAGOV[47]	Patients with angiographic coronary disease, currently on statins	-	(n=484) –56.3 mg/dL	-	(n=484) 0.2 mg/dL	-	-
FOURIER[48]	Patients with atherosclerotic CVD with LDL-C	(n=13,784)		(n=13,780)		-	-
	≥70 mg/dL, currently on statins	Between-group difference 61%					
TAUSSIG[49]	HoFH, on LLT	-	(n=106) –23.3%	-	-	-	-

*Least squares mean change from baseline; °mean of week 10 and week 12. LDL-C, low-density lipoproteins-cholesterol; Q2W, every 2 weeks; Q4W, every 4 weeks HoFH, homozygous familial hypercholesterolemia; HeFH, heterozygous familial hypercholesterolemia; CVD, cardiovascular disease; LLT, lipid-lowering therapy.

receiving LLT.[43] Patients were randomized to evolocumab 420 mg or placebo Q4W, with evolocumab significantly reducing LDL-C at 12 weeks. Evolocumab has also been investigated in HeFH patients with elevated LDL-C despite intense LLT, in RUTHERFORD-2, compared with placebo, evolocumab led to significant reductions in mean LDL-C at week 12 and was well tolerated, with rates of adverse events similar to placebo.[44]

The LAPLACE-2 study evaluated evolocumab versus placebo or ezetimibe in patients randomized to different background statin therapies.[45] Reductions in LDL-C were similar across statin groups for evolocumab administered every 2 weeks and monthly.

Patients from 12 phase II or III parent trials of evolocumab were enrolled into one of two long-term extension studies (OSLER and OSLER-2) and randomized to standard care plus evolocumab 420 mg Q4W or standard care alone in OLSER-1, with OLSER-2 patients given a choice of 140 mg Q2Wor 420 mg Q4W. Evolocumab had a 12-week reduction in LDL-C of 61% compared with standard care, with this reduction sustained through to 48 weeks (58%).[46]

In terms of LDL-C level reduction with a PCSK9 inhibitor leading to a reduction in cardiovascular events, in the OSLER studies, patients in the evolocumab group had a significantly lower rate of all cardiovascular events than patients receiving standard therapy (Kaplan-Meier estimates at 1 year, 0.95% and 2.18%, respectively; hazard ratio, 0.47).[46] The GLAGOV study, which enrolled 968 patients presenting for coronary angiography, found that patients receiving evolocumab achieved a lower mean time-weighted LDL-C, compared with patient receiving placebo. The primary efficacy endpoint of nominal change in percent atheroma volume from baseline to week 78 increased by 0.05% with placebo and decreased by 0.95% with evolocumab ($P<0.001$).[47] Furthermore, patients receiving evolocumab in the FOURIER study, a randomized placebo-controlled trial involving 27,500 high-risk patients with CVD receiving background statin therapy, had significantly reduced risk of the major cardiovascular events, compared with patients receiving placebo.[48]

In an interim analysis of the phase III, non-randomized, open-label TAUSSIG trial, which is investigating the long-term efficacy and safety of evolocumab, patients with HoFH who received stable LLT for at least 4 weeks, with or without apheresis, had a reduction in LDL-C after 12 weeks of evolocumab.[49] TAUSSIG is still ongoing and final results from this trial are needed to confirm this finding.

Marketed agents for homozygous familial hypercholesterolemia only

Lomitapide

Lomitapide, an inhibitor of MTP,[50] was approved in Europe in 2012 as adjunctive therapy to a low-fat diet and other LMTs with or without LDL apheresis in adult patients with HoFH.

In a multinational, phase III single-arm open-label study of lomitapide 5 mg/day to 60 mg/day for HoFH in 29 patients with elevated LDL-C despite LLT, including LDL apheresis, LDL cholesterol was reduced by 50% from baseline to week 26.[51] Of note, four patients had amino transaminase levels of more than five times the upper limit of normal, which resolved after dose reduction or temporary interruption of lomitapide. The extension of the phase III trial showed consistent findings with the original trial and indicated that lomitapide treatment in adjunct to other LLTs was highly effective in lowering LDL-C levels with acceptable tolerability and no new safety concerns.[52]

Mipomersen

Mipomersen is an antisense oligonucleotide that inhibits the synthesis of apo B, an essential component of LDL-C.[53] Mipomersen was approved in 2013 by the US FDA as an adjunct to lipid-lowering medications and diet to reduce LDL-C, apo B, total cholesterol, and non-HDL-C in patients with HoFH; it is not approved in Europe. Clinical trial data revealed consistent decreases in LDL-C with mipomersen in a range of patient populations (Table 3).[54-60]

There is evidence of an increased risk of transaminase elevations in patients receiving mipomersen. In an open-label, long-term efficacy and safety study of mipomersen, reduction in all atherosclerotic lipoproteins and an acceptable safety profile was sustained for up to 104 weeks in high-risk patient populations.[54]

The US FDA labelling information for both lomitapide and mipomersen carries a Black Box warning about the serious risk of liver toxicity.

Conclusions

Current management of hypercholesterolemia is challenging in patients with high cardiovascular risk and many patients do not achieve their therapeutic target despite maximal treatment with statins with or without other LMTs. Inadequate LDL-C control is associated with increased risk of cardiovascular-related events/mortality. Available evidence suggests that additional agents may have a role in the future of hypercholesterolemia management (Table 4). Results from the ODYSSEY OUTCOMES and FOURIER

Table 3. Summary of mipomersen clinical data: change in low-density lipoproteins-cholesterol levels from baseline.

Study	Patient population	Mipomersen dose (mg/week)	LDL-C change from baseline* Mipomersen	Placebo
Akdim *et al*., 2010[55]	Hypercholesterolemia on stable statins	30 to 400	(n = 49) –21% to –52%°,# (week 5)	(n=13) –3% (week 5)
Akdim *et al*., 2010[56]	HeFH on stable LLT	50 to 300	(n = 36) –11% to –34%° (week 6)	(n=8) 0% (week 6)
Raal *et al*., 2010[57]	HoFH, maximally tolerated LLT	200	(n=34) –25% (week 28)	(n=17) –3% (week 28)
McGowan *et al*., 2012[58]	Severe hypercholesterolemia on maximal statins	200	(n=39) –36% (week 28)	(n=18) +13% (week 28)
Thomas *et al.*, 2013[59]	Severe hypercholesterolemia at high CV risk	200	(n=101) –37% (week 28)	(n=50) –5% (week 28)
Visser *et al.*, 2012[60]	High-risk CV statin intolerant	200	(n=21) –47% (Week 28)	(n=12) –2% (week 28)

*Least squares mean change from baseline; °for doses of 100 mg/week or higher; #for patients who received mipomersen over a 5-week period. LDL-C, low-density lipoproteins-cholesterol; HeFH, heterozygous familial hypercholesterolemia; LLT, lipid-lowering therapy; CV, cardiovascular.

Table 4. Approved and proposed clinical role of novel lipid-modifying therapies in the high cardiovascular risk population based on current evidence.

Therapy	Approved role
Alirocumab	Indicated adjunct to diet and maximally tolerated statin therapy for treatment of adults with HeFH or clinical atherosclerotic CVD who require additional lowering of LDL-C
Evolocumab	Indicated adjunct to diet and maximally tolerated statin therapy for treatment of adults with HeFH or clinical atherosclerotic CVD who require additional lowering of LDL-C; indicated adjunct to other LDL lowering therapies (statins, ezetimibe, LDL apheresis) in patients with HoFH who require additional lowering of LDL-C
	Proposed role
Lomitapide	Adjunctive therapy in HoFH only
Mipomersen	HoFH only

HeFH, heterozygous familial hypercholesterolemia; CVD, cardiovascular disease; LDL-C, low-density lipoproteins-cholesterol; HoFH, homozygous familial hypercholesterolemia.

studies provided evidence for the efficacy of alirocumab and evolocumab in improving CVD outcomes in patients with elevated LDL-C. Lomitapide and mipomersen are approved for the treatment of HoFH, but their use in other hypercholesterolemias and dyslipidemias is not indicated. Novel agents, such as the PCSK9 inhibitors, will better meet the needs of this diverse population to allow more patients to achieve lipid goals and permit further reductions in cardiovascular risk.

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