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REVIEW

New and emerging lipid-modifying drugs to lower LDL cholesterol

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Abstract

Cardiovascular disease (CVD) represents the leading cause of death worldwide. The role of low-density lipoprotein-cholesterol (LDL-C) in the pathophysiology of atherosclerosis and CVD has been well recognized. Statins are the standard of care for the management of hypercholesterolaemia, and their effectiveness in lowering LDL-C and reducing CVD risk in both primary and secondary prevention has been well established. However, several patients fail to attain optimal LDL-C goals or are intolerant to statins, especially at high doses. PCSK9 inhibitors, bempedoic acid, inclisiran, ANGPTL3 inhibitors, PPARβ/δ agonists and LXR agonists are novel or upcoming LDL-C-lowering agents that have shown promising beneficial results. This review aims to present and discuss the current clinical and scientific data pertaining to the new and emerging lipid-modifying LDL-C-lowering drugs.

Keywords: ANGPTL3 inhibitors, bempedoic acid, cardiovascular disease, inclisiran, LDL-C-lowering, LXR agonists, PCSK9 inhibitors, PPARβ/δ agonists.

Citation

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Introduction

Cardiovascular disease (CVD) represents the most common cause of death worldwide, accounting for an estimated 17.8 million deaths in 2017. In addition, an estimated 43.9% of the US adult population is projected to have some form of CVD by 2030.[1,2]

The role of low-density lipoprotein cholesterol (LDL-C) in the pathogenesis of atherosclerosis and CVD has been well established. Clinical studies have demonstrated a proportional relationship between a reduction of LDL-C and a reduction in the risk of CVD.[3]

Statins are the standard of care for the management of hypercholesterolaemia, and there is extensive evidence supporting their effectiveness in lowering LDL-C and reducing CVD risk in both primary and secondary prevention. Statins limit intrahepatic production of cholesterol by competitively inhibiting 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, a key rate-limiting enzyme in the mevalonate pathway, which converts HMG-CoA into mevalonic acid, a cholesterol precursor. Statins alter the conformation of the enzyme when they bind to its active site, thus preventing HMG-CoA reductase from attaining a functional structure.[4] The reduction of cholesterol synthesis in hepatocytes leads to the upregulation of LDL receptors (LDLR) with ensuing increased cholesterol uptake by cells and lower cholesterol levels.[5]

In a large prospective meta-analysis of data from 90,056 participants in 14 randomized statin trials (4S, WOSCOPS, CARE, Post-CABG, AFCAPS/TexCAPS, LIPID, GISSI Prevention, LIPS, HPS, PROSPER, ALLHAT-LLT, ASCOT-LLA, ALERT, CARDS), statin therapy caused a 12% proportional reduction in all-cause mortality per mmol/L reduction in LDL-C, which reflected a 19% reduction in coronary mortality ($p<0.0001$). The corresponding reductions in myocardial infarction or coronary death, need for coronary revascularization, fatal or non-fatal stroke and any major vascular event were 23%, 24%, 17% and 21%, respectively ($p<0.0001$).[6]

Furthermore, there is evidence that the beneficial cardiovascular effects of statins extend beyond the lowering of LDL-C. In a randomized, double-blind, placebo-controlled, multicentre trial, 17,802 apparently healthy men and women with LDL-C levels of <130 mg/dL and high-sensitivity

C-reactive protein (hsCRP) levels of ≥2.0 mg/L were randomly assigned to receive rosuvastatin (20 mg daily) or placebo. The trial was stopped after a median follow-up period of 1.9 years. Rosuvastatin therapy (*versus* placebo) reduced the occurrence of the combined primary endpoint of myocardial infarction, stroke, arterial revascularization, hospitalization for unstable angina, or death from cardiovascular causes by 44% (p<0.00001). Rosuvastatin, as compared with placebo, reduced the rates of myocardial infarction, stroke, revascularization or unstable angina, the combined endpoint of myocardial infarction, stroke, or death from cardiovascular causes, and death from any cause by 54% (p=0.0002), 48% (p=0.002), 47% (p<0.00001), 47% (p<0.00001) and 20% (p=0.02), respectively.[7]

However, several patients fail to attain optimal LDL-C goals,[8,9] including patients with familial hypercholesterolaemia (FH) or patients with established coronary artery disease (CAD) that cannot achieve their LDL-C target despite high-intensity statin treatment. Besides, several patients exhibit intolerance to statins due to side effects, mostly myalgia and weakness, especially at high statin doses.[10]

Given the above, research has focused on the development of alternative LDL-C-lowering therapies with a benign side-effect profile, which (used alone or along with statin therapy) would allow for effective and durable lowering of LDL-C levels and a subsequent decrease in the risk of CVD.[11,12]

This narrative review aims to provide the current evidence regarding the newly approved LDL-C-lowering therapies as well as the clinical and scientific data pertaining to promising new and emerging lipid-modifying drugs that lower LDL-C.

Review

PCSK9 inhibitors

Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a serine protease expressed primarily in the liver but also found in other tissues, including pancreas, intestine, kidneys and brain.[13] The human *PCSK9* gene is located in the human chromosome 1p32.3 and is 22-kb in length, comprising 12 exons, encoding a 692 amino acid inactive glycoprotein, which undergoes an intramolecular self-catalytic cleavage in the endoplasmic reticulum. This auto-cleavage process of PCSK9 is crucial for both its activation and release from the endoplasmic reticulum.[11,14] PCSK9 binds to the LDLR and directs the receptors for lysosomal destruction, thus reducing their recycling and decreasing the removal rate of circulating LDL-C with a subsequent increase of the LDL-C levels in the blood.[11,15–19] Gain-of-function mutations of *PCSK9* in humans are linked to hypercholesterolaemia and elevated risk of CAD,[20,21] whereas loss-of-function mutations of *PCSK9* are linked to low LDL-C levels and reduced cardiovascular risk.[22]

In 2015, two PCSK9 inhibitors in the form of monoclonal antibodies to PCSK9 (evolocumab and alirocumab) were approved by the US FDA as add-on treatments to diet and maximally tolerated dose of statins for patients with FH or clinical atherosclerotic cardiovascular disease (ASCVD) who require additional lowering of LDL-C. PCSK9 inhibitors have been shown to markedly decrease LDL-C and are associated with a low incidence of adverse events.

In the Open-Label Study of Long-Term Evaluation against LDL Cholesterol 1 (OSLER-1) and 2 (OSLER-2), a total of 4465 patients with different degrees of cardiovascular risk were enrolled and were randomized to receive evolocumab or standard therapy. The results of these two studies were analysed and reported together. The results showed that, after 12 weeks of treatment, evolocumab, as compared to standard therapy, decreased LDL-C levels by 61% and this effect remained consistent over time. Furthermore, evolocumab raised high-density lipoprotein-cholesterol (HDL-C) and apolipoprotein A1 (ApoA1) levels by 7.0% and 4.2%, respectively (p<0.001 for both comparisons).[23]

The ODYSSEY LONG TERM trial was a double-blind, randomized, controlled trial that assessed the effects of alirocumab treatment for 78 weeks compared with placebo in 2341 patients at high risk of cardiovascular events, being treated with the maximum tolerated doses of statins.[24] Alirocumab treatment, as compared with placebo, led to an incremental 61.9% lowering of LDL-C. At week 24, 79.3% of patients treated with alirocumab, *versus* only 8.0% of those given placebo, attained an LDL-C level of <70 mg/dL (p<0.001). The LDL-C-lowering effect of alirocumab was consistent from week 4 to week 78 of the trial. Furthermore, treatment with alirocumab, as compared with placebo, decreased levels of apolipoprotein B (ApoB), total cholesterol, non-HDL-C, lipoprotein(a) and fasting triglycerides by 54%, 37.5%, 52.3%, 25.6% and 17.3%, respectively. Moreover, alirocumab, as compared with placebo, increased levels of HDL-C and ApoA1 by 4.6% and 2.9%, respectively.[24,25]

In addition, PCSK9 inhibition was demonstrated to be efficacious in patients who are intolerant to statins. In a clinical study, which enrolled patients with statin intolerance at moderate-to-high cardiovascular risk, alirocumab treatment led to a mean LDL-C reduction of 45.0%, whereas ezetimibe reduced mean LDL-C by 14.6% (mean difference 30.4%, p<0.0001). The incidence of adverse events related to skeletal muscles was lower in the group of patients treated with alirocumab as compared to another group of patients who were rechallenged with atorvastatin (hazard ratio 0.61, p=0.042).[25,26]

On the other hand, the LDL-C-lowering effect of PCSK9 inhibitors is also associated with an improvement in cardiovascular outcomes. In the FOURIER trial, a randomized, double-blind, placebo-controlled trial that enrolled 27,564 patients aged 40–85 years with stable ASCVD and additional risk factors, treatment with evolocumab reduced the primary endpoint of the trial (composite of cardiovascular death, myocardial infarction, stroke, coronary revascularization or hospital admission for unstable angina) by 15% and reduced the key secondary endpoint (composite of cardiovascular death, myocardial infarction or stroke) by 20% over an average

follow-up period of 2.2 years. It is also important to note that, beyond 12 months, the decrease in the incidence of the key secondary outcome with evolocumab was 25% as compared to 16% during the first 12 months. Concerning efficacy, the results were consistent across subgroups, including sex and quartiles of baseline LDL-C, and the effect appeared to increase over time.[27]

Furthermore, a prespecified secondary analysis of the FOURIER trial, which addressed the concern of possible safety implications due to the markedly low LDL-C concentrations seen with PCSK9 inhibition, clearly demonstrated that there was a monotonic relationship between achieved LDL-C and major cardiovascular outcomes down to LDL-C levels <0.2 mmol/L (7.7 mg/dL). Moreover, there were no safety concerns associated with very low LDL-C levels over a median of 2.2 years. These data support more aggressive lowering of LDL-C in patients with CVD to well below current recommendations.[28]

Another prespecified analysis of the FOURIER trial, which assessed the efficacy and safety of evolocumab by diabetes mellitus (DM) status and the effect of evolocumab on glycaemia and risk of developing DM, demonstrated that evolocumab significantly decreased the risk of CVD in patients with and without DM (HR 0.83 and 0.87, respectively) and did not augment the risk of development of new-onset DM nor did it worsen glycaemia.[29]

The results of the FOURIER trial on cardiovascular outcomes were corroborated by the results of the ODYSSEY OUTCOMES trial. In the ODYSSEY OUTCOMES trial, a multicentre, randomized, double-blind, placebo-controlled trial, which enrolled 18,924 patients who had an acute coronary syndrome 1–12 months earlier, LDL-C levels of ≥70 mg/dL, non-HDL-C levels of ≥100 mg/dL, or ApoB levels of ≥80 mg/dL, and were receiving statin therapy at a high-intensity dose or at the maximum tolerated dose, treatment with alirocumab reduced the primary endpoint of the trial (composite of death from coronary heart disease, non-fatal myocardial infarction, fatal or non-fatal ischemic stroke, or unstable angina requiring hospitalization) by 15% and reduced deaths from any cause by 15% over a median follow-up period of 2.8 years. Of note, the absolute benefit of alirocumab with respect to the composite primary endpoint was greater amongst patients with a baseline LDL-C level of ≥100 mg/dL.[30]

Apart from the marked LDL-C reduction and improvement in cardiovascular outcomes, PCSK9 inhibitors also have an excellent safety profile and are well tolerated.[30] Common adverse effects of PCSK9 inhibitors are usually mild and include nasopharyngitis, injection-site reactions and upper respiratory tract infections.[31,32]

In a large systematic review and network meta-analysis, which included 30 trials with a total of 59,026 patients and provided an indirect comparison of the efficacy and safety of alirocumab *versus* evolocumab, it was shown that alirocumab, as compared with evolocumab, was associated with a significant 20% reduction in all-cause death. Of note, alirocumab was associated with a 27% increased risk of injection-site reactions compared to evolocumab. There were no significant differences demonstrated in the rates of myocardial infarction, cardiovascular death, stroke or coronary revascularization between the two agents in this study.[33]

Earlier trials of PCSK9 inhibitors had raised a concern as they had shown a somewhat higher incidence of adverse neurocognitive events related to treatment with PCSK9 inhibitors as compared with placebo.[23,24] However, the subsequent FOURIER[27] and ODYSSEY OUTCOMES[30] clinical trials did not report a significant difference in the incidence of adverse neurocognitive events between patients treated with a PCSK9 inhibitor *versus* placebo. Furthermore, in order to specifically explore this issue, a randomized, double-blind, placebo-controlled, multicentre study (EBBINGHAUS study) was conducted, which included a subgroup of patients from the FOURIER trial and prospectively assessed the cognitive function in 1204 patients using the Cambridge Neuropsychological Test Automated Battery. The results of the EBBINGHAUS study demonstrated that there were no significant differences in cognitive function between patients receiving evolocumab *versus* placebo, in addition to statin therapy, over a median of 19 months. Moreover, in this study, no relation between levels of LDL-C and cognitive changes was observed.[34]

In addition, as mentioned earlier, in contrast to statins, clinical evidence shows that treatment with PCSK9 inhibitors provides powerful LDL-C-lowering and improved cardiovascular outcomes without an increase in the risk of DM.[29,35]

Thus, given the marked LDL-C-lowering, the improvement in cardiovascular outcomes and their excellent safety and tolerability profile, PCSK9 inhibitors have become a valuable addition to current lipid-modifying therapies, hence enhancing the armamentarium for the optimal management of cardiovascular risk in patients with dyslipidaemia.

Bempedoic acid

Bempedoic acid is a prodrug that is converted to an active metabolite (ETC-1002-CoA) by the enzyme very long-chain acyl-CoA synthetase 1 (ACSVL1), which is expressed primarily in the liver.[36] After activation, bempedoic acid inhibits adenosine triphosphate-citrate lyase (ACL). Inhibition of ACL leads to reduced levels of acetyl CoA at a point in the lipid synthesis pathway upstream of HMG-CoA reductase, the molecular target of statins. The resulting decreased cholesterol synthesis in the liver leads to the upregulation of LDLR and subsequent decrease in the levels of circulating LDL-C.[36–39] In addition, bempedoic acid has been also shown to activate adenosine monophosphate-activated protein kinase (AMPK). Activation of AMPK leads to an inhibitory phosphorylation of HMG-CoA reductase and to improved glucose homeostasis.[36–39]

In 2020, the use of bempedoic acid was approved by the US FDA as an adjunct to diet and maximally tolerated statin

therapy for the treatment of adults with heterozygous familial hypercholesterolaemia (HeFH) or established ASCVD who require additional lowering of LDL-C.

The LDL-C-lowering efficacy and safety of bempedoic acid have been demonstrated in several clinical trials. The CLEAR Harmony trial was a 52-week, randomized, double-blind, placebo-controlled, parallel-group, phase III trial that assessed the safety and efficacy of bempedoic acid to reduce LDL-C in 2230 patients with ASCVD, HeFH or both, who had LDL-C levels of ≥70 mg/dL whilst they were receiving maximally tolerated statin therapy with or without additional lipid-lowering therapy. The patients were randomly assigned in a 2:1 ratio to receive either bempedoic acid (at a dose of 180 mg once daily) or matching placebo. At week 12, bempedoic acid reduced the mean LDL-C level by 16.5% from baseline and by 18.1% *versus* placebo ($p<0.001$). The incidence of adverse events and serious adverse events did not differ substantially between the bempedoic acid and placebo groups during the intervention period, though the incidence of adverse events leading to discontinuation of the regimen and the incidence of gout was higher in the bempedoic acid group than in the placebo group (10.9% *versus* 7.1% and 1.2% *versus* 0.3%, respectively).[40]

The CLEAR Wisdom trial was a 52-week, phase III, randomized, double-blind, placebo-controlled clinical trial that enrolled 779 patients with ASCVD, HeFH or both, who had an LDL-C level of ≥70 mg/dL whilst they were receiving maximally tolerated lipid-lowering therapy, randomized in a 2:1 ratio to receive either bempedoic acid (at a dose of 180 mg once daily) or matching placebo. Bempedoic acid lowered LDL-C levels significantly more than placebo at week 12 (–15.1% *versus* 2.4%, respectively; difference, –17.4%; $p<0.001$). Furthermore, significant reductions with bempedoic acid *versus* placebo were observed at week 12 for non-HDL-C (–10.8% *versus* 2.3%; difference, –13.0%; $p<0.001$), total cholesterol (–9.9% *versus* 1.3%; difference, –11.2%; $p<0.001$), ApoB (–9.3% *versus* 3.7%; difference, –13.0%; $p<0.001$) and hsCRP (median, –18.7% *versus* –9.4%; difference, –8.7%; $p=0.04$). Common adverse events of bempedoic acid compared with placebo included nasopharyngitis (5.2% *versus* 5.1%, respectively), urinary tract infection (5.0% *versus* 1.9%, respectively) and hyperuricaemia (4.2% *versus* 1.9%, respectively).[41]

The CLEAR Serenity trial was a 24-week, phase III, double-blind, placebo-controlled clinical trial that evaluated the efficacy, safety and tolerability of bempedoic acid in 345 patients with hypercholesterolaemia (LDL-C ≥130 mg/dL for primary prevention patients and LDL-C ≥100 mg/dL for secondary prevention and HeFH patients), who were statin intolerant and required lipid-lowering therapy for primary or secondary prevention of cardiovascular events. The patients were randomly assigned in a 2:1 ratio to receive either bempedoic acid (180 mg once daily) or matching placebo. Treatment with bempedoic acid significantly reduced LDL-C from baseline to week 12 (placebo-corrected difference, –21.4%; $p<0.001$). Furthermore, significant reductions with bempedoic acid compared with placebo were also observed in non-HDL-C (–17.9%), total cholesterol (–14.8%), ApoB (–15.0%) and hsCRP (–24.3%; $p<0.001$ for all comparisons). Treatment with bempedoic acid was safe and well tolerated. The most common muscle-related adverse event was myalgia and occurred in 4.7% of patients who received bempedoic acid and in 7.2% of patients who received placebo. Thus, bempedoic acid appears to be a safe and effective LDL-C-lowering therapeutic option for patients who are intolerant to statins.[42]

The CLEAR Tranquility trial was a phase III, multicentre, randomized, double-blind, placebo-controlled study that enrolled 269 patients with a history of statin intolerance and LDL-C levels of ≥100 mg/dL whilst on stable lipid-modifying therapy. Following a 4-week ezetimibe (10 mg/day) run-in period, patients were randomly assigned in a 2:1 ratio to receive treatment with either bempedoic acid (180 mg) or matching placebo once daily added to ezetimibe 10 mg/day for 12 weeks. The primary endpoint was the percent change from baseline to week 12 in LDL-C. Treatment with bempedoic acid added to a background lipid-modifying therapy that included ezetimibe reduced LDL-C by 28.5% more than placebo ($p<0.001$; –23.5% bempedoic acid, +5.0% placebo). Furthermore, bempedoic acid, as compared with placebo, caused significant reductions in non-HDL-C (–23.6%), total cholesterol (–18.0%), ApoB (–19.3%) and hsCRP (–31.0%; $p<0.001$ for all comparisons). Treatment with bempedoic acid was well tolerated as rates of treatment-emergent adverse events, muscle-related adverse events and discontinuations were similar in the bempedoic acid and placebo treatment groups. Thus, bempedoic acid appears to be a safe and effective LDL-C-lowering therapeutic option complementary to ezetimibe for patients who are intolerant to statins.[43]

In another phase III, double-blind clinical trial that enrolled 301 adult patients at high risk of CVD due to ASCVD, HeFH or multiple CVD risk factors, patients were randomly assigned (2:2:2:1) to treatment with the fixed-dose combination, bempedoic acid (180 mg), ezetimibe (10 mg) or placebo added to stable background statin therapy for 12 weeks. The primary efficacy endpoint was the percentage change from baseline to week 12 in LDL-C. At week 12, the fixed-dose combination lowered LDL-C (–36.2%) significantly more than placebo (1.8%, placebo-corrected difference, –38.0%; $p<0.001$), ezetimibe alone (–23.2%; $p<0.001$) or bempedoic acid alone (–17.2%; $p<0.001$). Furthermore, the fixed-dose combination lowered LDL-C levels similarly across subgroups, including patients receiving high-intensity, other-intensity or no statin therapy. In addition, improvements with the fixed-dose combination were also observed in secondary efficacy endpoints, including hsCRP. Treatment with fixed-dose combination had a generally similar safety profile compared with bempedoic acid, ezetimibe or placebo. Thus, the bempedoic acid and ezetimibe fixed-dose combination appears to be a safe and effective LDL-C-lowering therapeutic option when added to maximally tolerated statin therapy in patients with hypercholesterolaemia and high CVD risk.[44]

In a systematic review and meta-analysis, which included 10 phase II and phase III randomized controlled trials with a total of 3,788 patients, it was demonstrated that bempedoic acid significantly reduced total cholesterol, non-HDL-C, LDL-C, LDL particle number, ApoB, HDL-C, HDL particle number and hsCRP by 14.94%, 18.17%, 22.94%, 20.67%, 15.18%, 5.83%, 3.21% and 27.03%, respectively. The levels of triglycerides and ApoA1 as well as the VLDL particle number did not change significantly with bempedoic acid treatment. Treatment with bempedoic acid, as compared with control therapy, was associated with higher rates of hyperuricaemia, elevated liver enzymes and elevated creatine kinase. On the other hand, treatment with bempedoic acid was associated with a significantly decreased risk of new onset or worsening DM.[45] In another systematic review and meta-analysis of four available phase II and phase III clinical studies, which included a total of 3369 participants and assessed the effect of bempedoic acid on serum uric acid and related outcomes, treatment with bempedoic acid, as compared with control therapy, significantly increased serum uric acid by an average of 0.73 mg/dL with an associated 3.56-fold increase in the incidence of gout. Bempedoic acid therapy was also associated with a slight but significant increase in serum creatinine by an average of 0.04 mg/dL.[46]

Given the above, bempedoic acid represents a useful addition to our LDL-C-lowering therapies in current practice. Notwithstanding, further long-term outcome trials are required to explore the longer-term safety of treatment with bempedoic acid and to definitely establish the effect of bempedoic acid in the reduction of cardiovascular risk. To that effect, CLEAR Outcomes is an ongoing randomized, double-blind, placebo-controlled trial that will assess the effects of bempedoic acid on the occurrence of major cardiovascular events in patients with, or at high risk of, CVD who are statin intolerant. The study started in November 2016 has enrolled 14,014 participants, its estimated average treatment duration is 3.75 years, and its primary completion date is estimated to be in August 2022.[47] The results of the CLEAR Outcomes trial will provide valuable information regarding the benefit of bempedoic acid in reducing major adverse cardiovascular events and improving outcomes in patients who are statin intolerant with, or at high risk of, ASCVD.

Inclisiran

Inclisiran is a long-acting synthetic small interfering RNA (siRNA) molecule that specifically inhibits the production of PCSK9 in the liver. siRNAs block the expression of certain genes with complementary nucleotide sequences by selectively silencing the translation of their complementary target messenger RNAs (mRNAs) via intracellular binding to RNA-induced silencing complexes in a sequence-specific manner. Thus, siRNAs affect the degradation of mRNA post-transcription, hence preventing translation. Inclisiran is a double-stranded small RNA that inhibits the transcription of *PCSK9*, thus limiting the production of PCSK9 in the hepatocytes. This leads to an upregulation of LDLR in the hepatocyte membranes and a subsequent reduction in circulating LDL-C levels. Inclisiran has emerged as a potential alternative to PCSK9 monoclonal antibody LDL-C-lowering therapy.[48–50]

Inclisiran was recently approved by the European Medicines Agency (EMA), and its use was authorized in the European Union for the treatment of adults with primary hypercholesterolaemia or mixed dyslipidaemia. Approval of inclisiran by the US FDA is pending.

The ORION programme is a composite of several worldwide trials with the goal of assessing the safety and efficacy of inclisiran in certain groups of individuals, including people at high risk of ASCVD and patients with established ASCVD or FH.

OPION-1 was a phase II, multicentre, double-blind, placebo-controlled, multiple ascending-dose trial of inclisiran that enrolled 501 patients at high risk of CVD with elevated LDL-C levels. Amongst the participants, 69% had established ASCVD, 6% had FH and 73% were on statin therapy. The greatest efficacy was achieved with the two-dose 300-mg regimen of inclisiran, which, at day 180, decreased LDL-C and PCSK9 levels by 52.6% and 69.1%, respectively. These reductions remained significant at day 240. The most frequent adverse events included injection-site reactions, myalgia, headache, fatigue, nasopharyngitis, back pain, hypertension, diarrhoea and dizziness. Injection-site reactions were observed in 4% and 7% of patients who received one dose and two doses of inclisiran, respectively.[51]

ORION-2 was a phase II, open-label, single-arm, multicentre pilot study that evaluated the safety, tolerability and efficacy of inclisiran in four patients with homozygous familial hypercholesterolaemia (HoFH). All four participants achieved significant, durable reductions of PCSK9 levels (48.7–83.6% at day 90 and 40.2–80.5% at day 180). Significant LDL-C reductions were observed in three of the four patients (11.7–33.1% at day 90 and 17.5–37.0% at day 180). No drug-related adverse events or injection-site reactions were reported.[52]

ORION-3 is an ongoing phase II, open-label, non-randomized, active-comparator extension trial of ORION-1 that will assess the efficacy, safety and tolerability of long-term dosing of inclisiran and evolocumab in 490 participants at high risk of CVD with elevated LDL-C levels. ORION-3 is expected to be completed in 2022.[53]

ORION-4 is an ongoing double-blind, randomized, placebo-controlled, phase III trial intended to be conducted at approximately 180 clinical sites in the United Kingdom and the United States and will assess the effects of inclisiran on clinical outcomes amongst an estimated 15,000 patients with ASCVD. The primary completion date of ORION-4 is estimated to be in 2026.[54]

ORION-5 is an ongoing two-part (double-blind placebo-controlled/open-label), multicentre study, that will evaluate safety, tolerability and efficacy of inclisiran in 56 patients with

HoFH. ORION-5 is estimated to be completed in September 2021.[55]

ORION-6 is a phase I, single-dose, open-label, parallel-group study expected to assess the pharmacokinetics, pharmacodynamics and safety of inclisiran in 24–32 patients with hepatic impairment compared with patients with normal hepatic function.[56]

ORION-7 was a phase I, single-dose, open-label trial that evaluated the safety, tolerability, pharmacokinetics and pharmacodynamics of a single dose of inclisiran in 31 participants with mild, moderate or severe renal impairment compared to participants with normal renal function.[57] The inclisiran-induced LDL-C reductions at day 60 were significant and similar for participants with normal renal function (57.6%±10.7%) and participants with mild (35.1%±13.5%), moderate (53.1%±21.3%) or severe (49.2%±26.6%) renal impairment (p=0.17 for participants with normal renal function *versus* participants with any renal impairment). In addition, the pharmacodynamic effects and safety profile of inclisiran were similar in study participants with normal and impaired renal function. No dose adjustments of inclisiran were required for patients with renal impairment.[58]

ORION-8 is an ongoing, global, multicentre extension study that will evaluate the efficacy, safety and tolerability of long-term dosing of inclisiran in 2991 participants with a high cardiovascular risk and elevated LDL-C. More specifically, ORION-8 will be an open label, long-term extension study in patients with ASCVD, ASCVD-risk equivalents, or FH (HeFH or HoFH) and elevated LDL-C despite maximum tolerated dose of LDL-C-lowering therapies.[59] The participants of ORION-8 will have completed any of the following inclisiran phase III lipid-lowering studies: ORION-9,[60] ORION-10,[61] ORION-11[61] or ORION-5.[55] ORION-8 is estimated to be completed in 2023.[59]

ORION-9 was a double-blind, randomized, placebo-controlled, phase III trial that assessed the effect of inclisiran on LDL-C in 482 patients with HeFH. At day 510, the mean changes in LDL-C levels were a reduction of 39.7% in the inclisiran group *versus* an increase of 8.2% in the placebo group (for a between-group difference of −47.9%). In addition, at day 510, the mean changes in PCSK9 levels were a reduction of 60.7% in the inclisiran group *versus* an increase of 17.7% in the placebo group (for a between-group difference of −78.4%). The time-averaged change in LDL-C between day 90 and day 540 was a reduction of 38.1% in the inclisiran group *versus* an increase of 6.2% in the placebo group (for a between-group difference of −44.3%). The incidence of adverse events and serious adverse events was similar in the two groups.[60]

ORION-10 and ORION-11 were two randomized, double-blind, placebo-controlled, parallel-group, phase III trials that evaluated the efficacy and safety of inclisiran over a period of 18 months in 1561 adults with ASCVD and LDL-C levels of ≥70 mg/dL (ORION-10) and in 1617 adults with ASCVD and LDL-C levels of ≥70 mg/dL or with an ASCVD-risk equivalent and LDL-C levels of ≥100 mg/dL (ORION-11). Most of the participants in these two trials were on statin therapy (89.2% of the participants in ORION-10 and 94.7% of the participants in ORION-11). At day 510, inclisiran treatment led to a reduction of LDL-C levels by 52.3% in ORION-10 and by 49.9% in ORION-11 with corresponding time-adjusted reductions of 53.8% and 49.2%, respectively. Moreover, at day 510, inclisiran treatment led to a reduction of PCSK9 levels by 69.8% in ORION-10 and by 63.6% in ORION-11 with corresponding between-group differences (*versus* placebo) of −83.3% and −79.3%, respectively. There was no significant difference observed in the incidence of adverse events in the inclisiran and placebo groups in both trials, though the incidence of injection-site reactions was higher in the inclisiran group.[61]

Lastly, ORION-12 is a phase I, randomized, placebo-controlled, double-blind, parallel-design study with an open-label and positive control that will assess the electrocardiographic effects of inclisiran (including its effects on QT interval) in 200 healthy volunteers.[56]

Given the above beneficial results of the completed phase III clinical trials, inclisiran has emerged as a promising new agent in the management of hypercholesterolaemia. Compared to other LDL-C-lowering agents, such as statins, ezetimibe and PCSK9 inhibitors, inclisiran offers an infrequent, convenient dosing of twice a year, whilst simultaneously providing a significant, durable LDL-C reduction, associated with a favourable side-effect profile. The results of the ongoing ORION-4 trial are keenly awaited as they will more definitely demonstrate the role of inclisiran in decreasing cardiovascular risk and improving clinical outcomes in patients with ASCVD.

ANGPTL3 inhibitors

Angiopoietin-like protein 3 (ANGPTL3) is a secretory protein exclusively produced in the liver and an important regulator of plasma lipid levels by inhibiting lipoprotein lipase (LPL)-mediated and endothelial lipase (EL)-mediated hydrolysis of triglycerides and phospholipids.[62,63]

It has been shown that reduced expression or inactivation of ANGPTL3 in mice reduces plasma triglyceride, LDL-C, HDL-C, and free fatty acid levels and protects from atherosclerosis.[63–66] In humans, loss-of-function mutations in the *ANGPTL3* gene lead to familial combined hypolipidaemia.[63,67,68] In the DiscovEHR human genetics study, it was again shown that patients with loss-of-function variants of the *ANGPTL3* gene have substantially reduced levels of LDL-C, triglycerides and HDL-C. Furthermore, the risk of CAD amongst patients with loss-of-function variants of the *ANGPTL3* gene was 41% lower than the risk in the general population despite the presence of low HDL-C levels.[69]

It has been well established that statins, cholesterol-absorption inhibitors, bempedoic acid, PCSK9 inhibitors and inclisiran lower plasma LDL-C levels by upregulating the expression of LDLR on hepatocytes; hence, their action largely depends on

the presence of functional LDLR. Therefore, the LDL-C-lowering response to these agents may be only limited in patients with HoFH due to the absence of fully functional LDLR.[70,71]

On the other hand, there is evidence that the both ANGPLT3 loss-of-function variants and the pharmacological inhibition of ANGPTL3 reduce LDL-C levels via a mechanism independent of LDLR function.[72,73] Thus, the pharmacological inhibition of ANGPTL3 may represent an attractive LDL-C-lowering therapeutic strategy for patients with HoFH.

Evinacumab is a fully human ANGPTL3-blocking monoclonal antibody. In an earlier phase II single group, open-label, proof-of-concept study involving nine patients with HoFH already receiving aggressive lipid-lowering regimens, including statins, ezetimibe, lomitapide, PCSK9 inhibitors or a portacaval shunt, treatment with evinacumab resulted in a mean reduction of LDL-C levels by 49%±23% at week 4, with an absolute decrease from baseline of 157±90 mg/dL. In addition, at week 4, treatment with evinacumab reduced ApoB, non-HDL-C, triglyceride and HDL-C levels by a mean of 46%±18%, 49%±22%, 47% and 36%±16%, respectively.[74]

In a double-blind, placebo-controlled, phase III trial, 65 patients with HoFH who were receiving stable lipid-lowering therapy were randomly assigned in a 2:1 ratio to receive an intravenous infusion of evinacumab (at a dose of 15 mg/kg) every 4 weeks or placebo. At week 24, the mean changes in LDL-C levels were a reduction of 47.1% in the evinacumab group *versus* an increase of 1.9% in the placebo group (for a between-group least-squares mean difference of −49.0%). The absolute between-group least-squares mean difference in the level of LDL-C was −132.1 mg/dL. Treatment with evinacumab, as compared with placebo, reduced LDL-C levels both in patients with null–null variants and virtually absent LDLR activity (−43.4% *versus* +16.2%) as well as in patients with non-null variants and impaired LDLR activity (−49.1% *versus* −3.8%). In addition, at week 24, evinacumab compared with placebo significantly reduced levels of ApoB and non-HDL-C (−41.4% *versus* −4.5% and −49.7% *versus* +2.0%, respectively, for a corresponding between-group least-squares mean difference of −36.9% and −51.7%, respectively). The incidence of adverse events was similar in the evinacumab and placebo groups.[75]

In another double-blind, placebo-controlled, phase II trial that was conducted at 85 sites across 20 countries, 272 patients with or without HeFH who had refractory hypercholesterolaemia (LDL-C >70 mg/dL for patients with clinical ASCVD or LDL-C >100 mg/dL for patients without clinical ASCVD) were randomly assigned to receive subcutaneous or intravenous evinacumab or placebo. The enrolled patients had hypercholesterolaemia that was refractory to treatment with a PCSK9 inhibitor and a statin at a maximum tolerated dose, with or without ezetimibe. At week 16, the differences in the least-squares mean change from baseline in the LDL-C level between the groups assigned to receive subcutaneous evinacumab at a dose of 450 mg weekly, 300 mg weekly and 300 mg every 2 weeks and the placebo group were −56.0%, −52.9% and −38.5%, respectively (p<0.001 for all comparisons). The differences between the groups assigned to receive intravenous evinacumab at a dose of 15 and 5 mg/kg and the placebo group were −50.5% (p<0.001) and −24.2%, respectively. The incidence of serious adverse events during the treatment period ranged from 3% to 16% across trial groups.[76]

Given the above, evinacumab has emerged as a promising new agent for the management of refractory hypercholesterolaemia, especially for patients with impaired or virtually absent LDLR activity/functionality. Evinacumab was recently approved by the US FDA and by EMA, and its use was authorized as an add-on treatment for patients aged 12 years and older with HoFH.

Another therapeutic strategy currently being pursued targeting ANGPTL3 is the inactivation of the *ANGPTL3* gene in the liver with the use of antisense oligonucleotides. ANGPTL3-L_{Rx} is a second-generation ligand-conjugated antisense oligonucleotide drug targeted to a region within the human *ANGPTL3* gene mRNA coding sequence. A randomized, double-blind, placebo-controlled, phase I clinical trial was designed to test the safety, side-effect profile, pharmacokinetics and pharmacodynamics of single ascending doses and multiple ascending doses of ANGPTL3-L_{Rx} in 44 healthy adults aged 18–65 years, randomly assigned in a 3:1 ratio to receive ANGPTL3-L_{Rx} or placebo. At day 43, participants who received therapy with ANGPTL3-L_{Rx} at a dose of 60 mg once weekly for a total of six doses presented a mean reduction in levels of triglycerides, LDL-C, ApoB, non-HDL-C and HDL-C of 50.4%, 32.9%, 22.2%, 36.6% and 26.7%, respectively. There were no serious adverse events and no injection-site reactions were documented during the trial.[77]

Further clinical trials are required to fully explore the potential of inactivating ANGPTL3 as a therapeutic target for dyslipidaemia and CVD.

PPARβ/δ agonists

Peroxisome proliferator-activated receptors (PPARs) are nuclear ligand-activated proteins that, once activated, regulate the transcription of target genes that control metabolism and energy equilibrium. PPARs regulate diverse aspects of lipid metabolism, thus playing a crucial role in lipid homeostasis. Three isotypes of PPARs have been described: α (NR1C1), β/δ (NR1C2) and γ (NR1C3). Fibrates are selective PPARα agonists used for the management of dyslipidaemia, whereas thiazolidinediones are potent PPARγ agonists used in the treatment of DM. PPARβ/δ agonists are not currently used in clinical practice, though some promising results have been reported with their use in early clinical trials.[39,78,79]

Seladelpar or MBX-8025 is a selective PPARβ/δ agonist, the use of which has shown some initial promising results in the management of dyslipidaemia/hypercholesterolaemia. In a randomized, double-blind, placebo-controlled, parallel group study conducted at 30 US sites, 181 overweight men and

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Table 1. Summary of the results of the clinical studies pertaining to statins and to novel LDL-C lowering agents.

Trial	Design	Intervention	Results
Baigent et al.[6]	Large prospective meta-analysis of 14 RCTs, including 90,056 participants	Statin therapy	Incidence of coronary heart disease and other major vascular events significantly reduced by 17–24%
JUPITER[7]	Double-blind, placebo-controlled, randomized, multicentre trial, including 17,802 healthy men and women with LDL-C <130 mg/dL and hsCRP ≥2 mg/dL	Rosuvastatin *versus* placebo, follow-up for a median of 1.9 years	In comparison to placebo, rosuvastatin lowered LDL-C levels by 50%, reduced hsCRP level by 37% and reduced incidence of cardiovascular events by 47–54% and death from any cause by 20%
OSLER-1 and OSLER-2[23]	Two-open label, randomized trials with 4465 patients with different degrees of cardiovascular risk having completed 1 of 12 parent trials of evolocumab	Evolocumab + standard therapy *versus* standard therapy alone, follow-up for a median of 11.1 months	At week 12, in the evolocumab group, LDL-C levels decreased by 61%, whereas HDL-C and Apo-A1 levels increased by 7.0% and 4.2%, respectively, as compared to standard therapy alone
ODYSSEY LONG TERM[24]	Multinational double-blind, phase III RCT, involving 2341 patients with LDL-C ≥70 mg/dL at high risk of cardiovascular events being treated with the maximum tolerated doses of statins	Alirocumab *versus* placebo for a total of 78 weeks	In the alirocumab group, there was 61.9% decrease of LDL-C, with the treatment effect remaining consistent over a 78-week period Alirocumab decreased levels of ApoB (54%), total cholesterol (37.5%), non-HDL-C (52.3%), Lp(a) (25.6%) and triglycerides (17.3%) Alirocumab increased HDL-C (4.6%) and ApoA1 (2.9%)
ODYSSEY ALTERNATIVE[26]	Double-blind, double-dummy, active-controlled, parallel-group, randomized phase III study, involving 314 patients at moderate or high CVD risk, with statin intolerance, confirmed by statin rechallenge arm	Alirocumab or ezetimibe or atorvastatin *versus* placebo for 24 weeks	Alirocumab led to a mean LDL-C reduction of 45.0% as compared to ezetimibe (14.6%) Decreased muscle symptoms and drug-discontinuation rates in the alirocumab group compared to the atorvastatin group (hazard ratio: 0.61, p=0.042)
FOURIER[27]	Double-blind, placebo-controlled, multinational, phase III RCT, involving 27,564 patients with ASCVD and LDL-C ≥70 mg/dL or non-HDL-C ≥100 mg/dL on statin therapy	Evolocumab *versus* placebo for a median duration of 2.2 years	Evolocumab decreased cardiovascular events by 15–20% as compared to placebo Increased injection-site reactions with evolocumab *versus* placebo (2.1% *versus* 1.6%) Consistent findings amongst subgroups, effects increased over time
Prespecified analysis of FOURIER[28]	Prespecified secondary analysis of 25,982 patients from the FOURIER trial that addressed the concern of possible safety implications due to the markedly low LDL-C concentrations seen with PCSK9 inhibition	Evolocumab *versus* placebo for a median duration of 2.2 years	Significant monotonic relationship between low LDL-C concentration (≤0.2 mmol/L) and low risk of cardiovascular events (primary and secondary endpoints) No safety concerns raised over very low LDL-C levels
Prespecified analysis of FOURIER[29]	Double-blind, prespecified secondary analysis of the FOURIER trial investigating the effect of evolocumab on cardiovascular events by diabetes status, on glycaemia and risk of developing diabetes	Evolocumab *versus* placebo for a median duration of 2.2 years	Evolocumab significantly decreased the risk of CVD in patients with or without DM (hazard ratio 0.83 and 0.87, respectively) Evolocumab did not increase new-onset DM, HbA1c or FPG

(Continued)

Table 1. (*Continued*)

Trial	Design	Intervention	Results
ODYSSEY OUTCOMES[30]	Double-blind, placebo-controlled, randomized, multicentred trial with 18,924 patients who had an ACS 1–12 months earlier, LDL-C ≥70 mg/dL, non-HDL-C ≥100 mg/dL or an ApoB level ≥80 mg/dL, on high-intensity statin therapy or at the maximum tolerated dose of statin	Alirocumab *versus* placebo for a median duration of 2.8 years	In the group of alirocumab, reduction of cardiovascular events and death of any cause by 15%, as compared to placebo Absolute benefit increased when baseline LDL-C ≥100 mg/dL Similar adverse effects, except for the injection-site reactions (alirocumab: 3.8% *versus* placebo: 2.1%)
Guedeney et al.[33]	Systematic review and network meta-analysis of 30 randomized trials comparing alirocumab to evolocumab, with a total of 59,026 patients	Alirocumab *versus* evolocumab with a mean weighted follow-up of 2.5 years	Alirocumab reduced all-cause death by 20%, in comparison to evolocumab 27% increased injection-site reactions due to alirocumab use compared to evolocumab No significant differences in cardiovascular events
EBBINGHAUS[34]	Double-blind, placebo-controlled, randomized, multicentre phase III study including 1204 patients from the FOURIER trial	Evolocumab *versus* placebo for a median duration of 19 months	No significant difference in cognitive function amongst patients receiving evolocumab *versus* placebo No relation between LDL-C levels and cognitive changes
CLEAR Harmony[40]	Double-blind, placebo-controlled, parallel-group, randomized phase III trial, including 2230 patients with ASCVD and/or HeFH, LDL-C ≥70 mg/dL whilst receiving maximum tolerated dose of statin therapy	Bempedoic acid *versus* matching placebo for a median duration of 52 weeks	At week 12 in the group of bempedoic acid, the mean LDL-C level decreased by 16.5% from baseline and by 18.1% compared to placebo No significant difference with regard to the adverse effects between the bempedoic acid and placebo groups; however, bempedoic acid led to higher incidence of adverse events leading to discontinuation of the regimen and gout (10.9% *versus* 7.1% and 1.2% *versus* 0.3%)
CLEAR Wisdom[41]	Double-blind, placebo-controlled, randomized, phase III trial, including 779 patients with ASCVD and/or HeFH, LDL-C ≥70 mg/dL whilst receiving maximum tolerated dose of statin therapy	Bempedoic acid *versus* matching placebo for a median duration of 52 weeks	At week 12, significant reduction of LDL-C levels when bempedoic acid was administered *versus* placebo (–15.1% *versus* 2.4%, respectively; difference, –17.4%)
CLEAR Serenity[42]	Double-blind, placebo-controlled, randomized, phase III clinical trial in 345 participants who were statin intolerant with hypercholesterolaemia who required lipid-lowering therapy	Bempedoic acid *versus* matching placebo for a median duration of 24 weeks	LDL-C levels were significantly reduced from baseline to week 12 when bempedoic acid was administered (placebo-corrected difference, –21.4%) Significant reduction with bempedoic acid *versus* placebo in levels of non-HDL-C (–17.9%), total cholesterol (–14.8%), ApoB (–15.0%) and hsCRP (–24.3%) Bempedoic acid safe and well-tolerated, less myalgias *versus* placebo (4.7% *versus* 7.2%, respectively)

(Continued)

Table 1. (*Continued*)

Trial	Design	Intervention	Results
CLEAR Tranquility[43]	Double-blind, placebo-controlled, parallel-group, randomized, multicentre, phase III clinical trial including 269 participants who were statin intolerant with hypercholesterolaemia already on stable lipid-lowering therapy	Ezetimibe during a 4-week run-in phase, followed by bempedoic acid *versus* placebo administration for 12 weeks	Treatment with bempedoic acid reduced LDL-C by 28.5%, compared to placebo Significant reduction with bempedoic acid *versus* placebo in levels of non-HDL-C (–23.6%), total cholesterol (–18.0%), ApoB (–19.3%) and hsCRP (–31.0%) Bempedoic acid + ezetimibe proved to be safe and effective, similar adverse effects compared to placebo (48.6% *versus* 44.8%, respectively)
Ballantyne et al.[44]	Double-blind, placebo-controlled, randomized, multicentre, phase III clinical trial enrolling 301 patients at high risk of CVD due to ASCVD, HeFH or multiple CVD risk factors, on maximum tolerated statin therapy	Bempedoic acid + ezetimibe *versus* Bempedoic acid alone *versus* Ezetimibe alone *versus* Placebo for 12 weeks	The drug combination lowered LDL-C levels (–36.2%) significantly more than bempedoic acid alone (–17.2%), ezetimibe alone (–23.2%) or placebo (+1.8%) Similar effect of the combination on subgroups
Cicero et al.[45]	Systematic review and meta-analysis of 10 phase II and III randomized controlled trials on bempedoic acid with a total of 3788 patients	Bempedoic acid *versus* control therapy	Bempedoic acid significantly reduced total cholesterol, non-HDL-C, LDL-C, LDL particle number, ApoB, HDL-C, HDL particle number, and hsCRP by 14.94%, 18.17%, 22.94%, 20.67%, 15.18%, 5.83%, 3.21% and 27.03%, respectively, though did not affect the level of triglycerides, ApoA1 and the VLDL particle number Decreased risk of new onset or worsening diabetes
Cicero et al.[46]	Systematic review and meta-analysis of four phase II and III RCTs on bempedoic acid with a total of 3369 patients	Bempedoic acid *versus* control therapy	Uric acid increased by an average of 0.73 mg/dL with a resultant 3.56-fold increase in gout Slight, yet significant increase in serum creatinine by an average of 0.04 mg/dL
CLEAR Outcomes[47]	Ongoing double-blind, placebo-controlled RCT, enrolling 14,014 participants	Bempedoic acid for 3.75 years	The trial will assess the effects of bempedoic acid on cardiovascular events in patients who are statin intolerant and are predisposed to or with CVD Ongoing – Estimated completion date: August 2022
ORION-1[51]	Double-blind, placebo-controlled, multicentre, phase II multiple ascending-dose trial enrolling 501 patients with elevated LDL-C levels, at high risk of CVD	Inclisiran *versus* placebo for 240 days	At day 180, the greatest efficacy was observed with the two-dose 300 mg regimen of inclisiran, leading to a reduction of LDL-C and PCSK9 levels by 52.6% and 69.1%, respectively
ORION-2[52]	Open-label, single-arm, multicentre proof-of-concept study conducted in four (4) patients with HoFH receiving maximum tolerated dose of lipid lowering therapy	Inclisiran	Significant decrease in PCSK9; 48.7–83.6% at day 90, and 40.2–80.5% at day 180 Only one participant failed to achieve a reduction in LDL-C

(Continued)

Table 1. (*Continued*)

Trial	Design	Intervention	Results
ORION-3[53]	Ongoing phase II, open-label, non-randomized, active-comparator extension trial of ORION-1, enrolling 490 patients with elevated levels of LDL-C and high risk of CVD	Inclisiran *versus* evolocumab	The trial will assess the efficacy, safety and tolerability of long-term dosing of inclisiran and evolocumab Ongoing – Estimated completion date: February 2022
ORION-4[54]	Ongoing double-blind, placebo-controlled, randomized, phase III trial, enrolling 15,000 participants with pre-existing atherosclerotic disease	Inclisiran *versus* placebo	The trial will assess the effects of inclisiran on clinical outcomes. Ongoing – Estimated primary completion date: July 2026 Estimated study completion date: December 2049
ORION-5[55]	Ongoing two part, double-blind, placebo-controlled/ open-label, multicentre phase II study in 56 patients with HoFH	Inclisiran *versus* placebo	The trial will assess the efficacy, safety and tolerability of inclisiran in patients with HoFH Ongoing – Estimated completion date: September 2021
ORION-6[56]	Scheduled single-dose, open-label, parallel-group phase I study including 24–32 patients with and without hepatic impairment	Inclisiran	The trial will assess the pharmacokinetics, pharmacodynamics and safety of inclisiran in patients with or without normal hepatic function
ORION-7[57,58]	Single-dose, open-label phase I trial enrolling 31 participants with mild, moderate or severe renal impairment or normal renal function	Inclisiran	At day 60, LDL-C was significantly reduced in participants with normal renal function (57.6%±10.7%), and mild (35.1%±13.5%), moderate (53.1%±21.3%) or severe (49.2%±26.6%) renal impairment Similar pharmacodynamics and safety in all participants Dose adjustment was not required in participants with renal dysfunction
ORION-8[59]	Ongoing open-label, global, multicentre, long-term extension study enrolling 2991 patients with high levels of LDL-C and high risk of CVD or ASCVD-risk equivalent	Inclisiran	The trial will assess the effect of long-term dosing of Inclisiran in patients with high CV risk and elevated LDL-C Ongoing – Estimated completion date: February 2023
ORION-9[60]	Double-blind, randomized, placebo-controlled, phase III trial including 482 patients with HeFH	Inclisiran *versus* placebo	At day 510, reduction of LDL-C levels by 39.7% in the inclisiran group *versus* 8.2% in the placebo group Time-average change between day 90 and 540 was –38.1% for the inclisiran group and +6.2% in the placebo group At day 510, reduction of PCSK9 by 60.7% in the inclisiran group *versus* 17.7% in the placebo group Similar adverse effects between the two groups

(Continued)

Table 1. (*Continued*)

Trial	Design	Intervention	Results
ORION-10[61]	Double-blind, placebo-controlled, parallel-group, randomized phase III trial enrolling 1561 patients with ASCVD and an LDL-C level ≥70 mg/dL, the majority of whom were on statin therapy	Inclisiran *versus* placebo for 540 days	At day 510, inclisiran administration achieved a decrease of 52.3% in LDL-C levels, with a corresponding time-adjusted reduction of 53.8% At day 510, PCSK9 levels decreased by 69.8% with a corresponding between-group difference (*versus* placebo) of 83.3% The incidence of adverse effects was similar between the inclisiran and the placebo groups, though injection-site reactions were more frequent with inclisiran than placebo (2.6% *versus* 0.9%)
ORION-11[61]	Double-blind, placebo-controlled, parallel-group, randomized phase III trial enrolling 1617 patients with an ASCVD-risk equivalent and an LDL-C level ≥100 mg/dL, the majority of whom were on statin therapy	Inclisiran *versus* placebo for 540 days	At day 510, inclisiran administration achieved a decrease of 49.9% in LDL-C levels, with a corresponding time-adjusted reduction of 49.2% At day 510, PCSK9 levels decreased by 63.6% with a corresponding between-group difference (*versus* placebo) of 79.3% The incidence of adverse effects was similar between the inclisiran and the placebo groups, though injection-site reactions were more frequent with inclisiran than placebo (4.7% *versus* 0.5%)
ORION-12[56]	Scheduled double-blind, placebo-controlled, parallel-group, open-label, randomized phase I study with a positive control including 200 healthy patients	Inclisiran *versus* placebo	The trial will assess the electrocardiographic effects of inclisiran in healthy participants
Gaudet et al.[74]	Single-group, open-label, proof-of-concept phase II study including nine patients with HoFH on aggressive lipid-lowering regimens	Evinacumab for 4 weeks	Evinacumab led to a mean reduction of LDL-C levels by 49±23% at week 4 with an absolute decrease from baseline of 157±90 mg/dL At week 4, evinacumab reduced ApoB, non-HDL-C, triglyceride and HDL-C levels by a mean of 46±18%, 49±22%, 47% and 36±16%, respectively
Raal et al.[75]	Double-blind, placebo-controlled, phase III trial enrolling 65 patients with HoFH on stable lipid-lowering regimen	Evinacumab *versus* placebo every 4 weeks for 24 weeks	In the evinacumab group, reduction of LDL-C levels by an average of 47.1% *versus* increase of LDL-C levels by 1.9% in the placebo group Evinacumab reduced LDL-C in both patients with null-null variants and patients with non-null variants, as compared to placebo (−43.4% *versus* +16.2% and −49.1% *versus* −3.8%, respectively)

(Continued)

Table 1. (*Continued*)

Trial	Design	Intervention	Results
Raal et al.[75] (*Cont*)			Significant reduction of ApoB and non-HDL-C levels (–41.4% *versus* –4.5% and –49.7% *versus* +2.0%, respectively) Similar incidence of adverse effects
Rosenson et al.[76]	Double-blind, placebo-controlled, multicentre, randomized phase III trial including 272 patients with refractory hypercholesterolaemia (LDL-C ≥70 mg/dL with clinical ASCVD or LDL-C ≥100 mg/dL without clinical ASCVD), resistant to PCSK9 inhibitor and a maximum tolerated dose of statin ± ezetimibe regimen	Evinacumab SC or IV *versus* placebo for 16 weeks	At week 16, the differences in the least-squares mean change from baseline in the LDL-C levels between the groups receiving SC evinacumab and placebo ranged from –38.5% to –56.0%, depending on the dosing regimen The differences between the groups receiving IV evinacumab and placebo ranged from –24.2% to –50.5%, depending on the administered dose Incidence of serious adverse events during the treatment period ranged from 3% to 16%
Graham et al.[77]	Double-blind, placebo-controlled, randomized phase I clinical trial carried out in 44 healthy adults	ANGPTL3-L_{RX} *versus* placebo for 6 weeks	At day 43, in the ANGPTL3-L_{Rx} group there was a mean reduction in levels of triglycerides, LDL-C, ApoB, non-HDL-C, and HDL-C of 50.4%, 32.9%, 22.2%, 36.6% and 26.7%, respectively No serious adverse events and no injection-site reactions
Bays et al.[80] and Choi et al.[81]	Double-blind, placebo-controlled, parallel-group, randomized study of 181 patients with mixed dyslipidaemia Double-blind, placebo-controlled, multicentre, parallel group, randomized trial including non-diabetic overweight or obese individuals with mixed dyslipidaemia	Once daily placebo, or atorvastatin 20 mg, or MBX-8025 at 50 or 100 mg alone or combined with atorvastatin for 8 weeks	As compared to placebo, treatment with MBX-8025 alone or in combination with atorvastatin reduced LDL-C by 18–43%, ApoB by 20–38%, non-HDL-C by 18–41%, triglycerides by 26–30%, free fatty acids by 16–28%, and hsCRP by 43–72% Furthermore, treatment with MBX-8025 alone or in combination with atorvastatin raised HDL-C by 1–12% and also reduced the number of patients with metabolic syndrome and a preponderance of small LDL particles Treatment considered safe and well tolerated Treatment with MBX-8025 resulted in reductions of small and very small LDL particles and raised levels of large LDL particles Reversal of the small-dense, more atherogenic LDL phenotype in approximately 90% of the participants
Gaudet et al.[82]	Open label, multicentre, non-controlled, monthly dose escalation study carried out in 13 patients with genetically confirmed HoFH receiving maximum tolerated lipid-lowering therapy	MBX-8025	42% manifested a ≥20% reduction in LDL-C levels, whereas the overall mean reduction in LDL-C levels was 10% with no clear dose response Unexpectedly increased PCSK9 levels, yet to be explained Safe and effective intervention

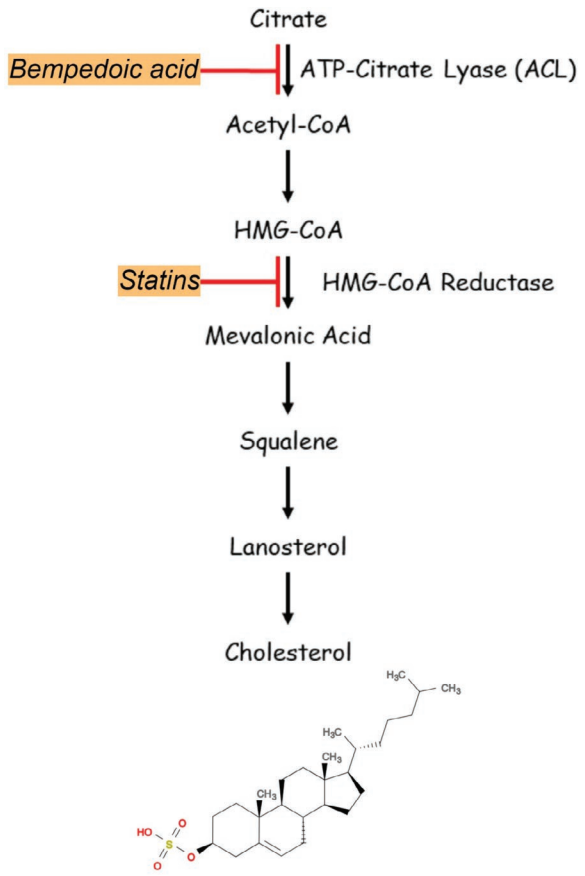
(Continued)

Table 1. (*Continued*)

Trial	Design	Intervention	Results
Quinet et al.[86]	Non-human primates	WAY-252623 (LXR-623)	Significant reduction of total cholesterol and LDL-C levels by 50–55% and 70–77%, respectively Enhanced expression of the target genes ABCA1/G1 in peripheral blood cells
Xu et al.[79] and Katz et al.[85]	First-in human double-blind, placebo-controlled, inpatient, ascending-dose randomized study	WAY-252623 (LXR-623) *versus* placebo	Serious adverse events related to the central nervous system, leading to cessation of further development of LXR-623
Kirchgessner et al.[90]	Non-human primates	BMS-779788 *versus* full pan agonist	Reduction of lipogenic potential and improved plasma lipid profile *versus* full pan agonist Supports concept of restricting LXRα activity to avoid the undesirable lipid effects of LXR agonists
Li et al.[91]	In vitro cell study	IMB-808	IMB-808 effectively increased the expressing quantity of genes related to RCT, as well as those associated with cholesterol metabolism pathway in multiple cell lines Additionally, IMB-808 remarkably promoted cholesterol efflux from RAW264.7 and THP-1 macrophage cells and reduced cellular lipid accumulation accordingly IMB-808 might be used as a promising therapeutic agent for the prospective treatment of atherosclerosis in the future

ABCA1, ATP-binding cassette transporter 1; ACS, acute coronary syndrome; ApoA1, apolipoprotein A1; ApoB, apolipoprotein B; ASCVD, atherosclerotic cardiovascular disease; ATV, atorvastatin; CLEAR, cholesterol lowering via bempedoic acid, an ACL-inhibiting regimen; CVD, cardiovascular disease; DM, diabetes mellitus; FPG, fasting plasma glucose; HbA1c, haemoglobin A1c; HeFH, heterozygous familial hypercholesterolaemia; HoFH, homozygous familial hypercholesterolaemia; hsCRP, high-sensitivity C-reactive protein; LDL-C, low density lipoprotein cholesterol; Lp(a), lipoprotein (a); LXR, liver X receptors; non-HDL-C, non-high density lipoprotein cholesterol; OSLER-1/-2, Open-Label Study of Long-Term Evaluation against LDL Cholesterol-1/-2; PCSK9, proprotein convertase subtilisin/kexin type 9; RCT, randomized controlled trial; VLDL, very low density lipoprotein.

Figure 1. Mechanism of action of statins and bempedoic acid.



ACL, adenosine triphosphate-citrate lyase; CoA, coenzyme A; HMG, 3-hydroxy-3-methylglutaryl.

women with mixed dyslipidaemia were randomly assigned to receive once daily placebo, atorvastatin 20 mg, or MBX-8025 at 50 or 100 mg alone or combined with atorvastatin for 8 weeks. In this study, as compared with placebo, treatment with MBX-8025 alone or in combination with atorvastatin reduced LDL-C by 18–43%, ApoB by 20–38%, non-HDL-C by 18–41%, triglycerides by 26–30%, free fatty acids by 16–28% and hsCRP by 43–72% ($p<0.05$ for all comparisons). In addition, treatment with MBX-8025 alone or in combination with atorvastatin raised HDL-C by 1–12% and reduced the number of patients with the metabolic syndrome and a preponderance of small LDL particles.[80] More specifically, treatment with MBX-8025 resulted in reductions of small plus very small LDL particles and raised levels of large LDL particles, with a concomitant reduction in large very-low-density lipoprotein particles and an increase in LDL peak diameter. This led to a reversal of the small, dense atherogenic LDL phenotype (LDL pattern B) in approximately 90% of participants.[81] Treatment with MBX-8025 was in general safe and well tolerated.[80]

In a 12-week, phase II, open label, multicentre, non-controlled, monthly dose escalation study that assessed the effect of MBX-8025 on LDL-C in 13 patients with HoFH receiving stable maximal lipid lowering therapy, 42% of participants had a ≥20% reduction in LDL-C levels, whereas, overall, the mean reduction in LDL-C levels was 10% with no clear dose response. There was an unexpected increase in PCSK9 levels during treatment, which requires further investigation. MBX-8025 was generally well tolerated.[82]

Although the initial results with the use of MBX-8025 appear promising, further large clinical studies are required to more definitely assess the benefits of treatment with MBX-8025 (or another PPARβ/δ agonist) in the reduction of cardiovascular risk and improvement of clinical outcomes.

LXR agonists

Liver X receptors (LXR) are ligand-activated transcription factors that play a major role in the regulation of gene expression involved in diverse cellular functions but especially in lipid and bile acid metabolism and cholesterol homeostasis.[38,83,84]

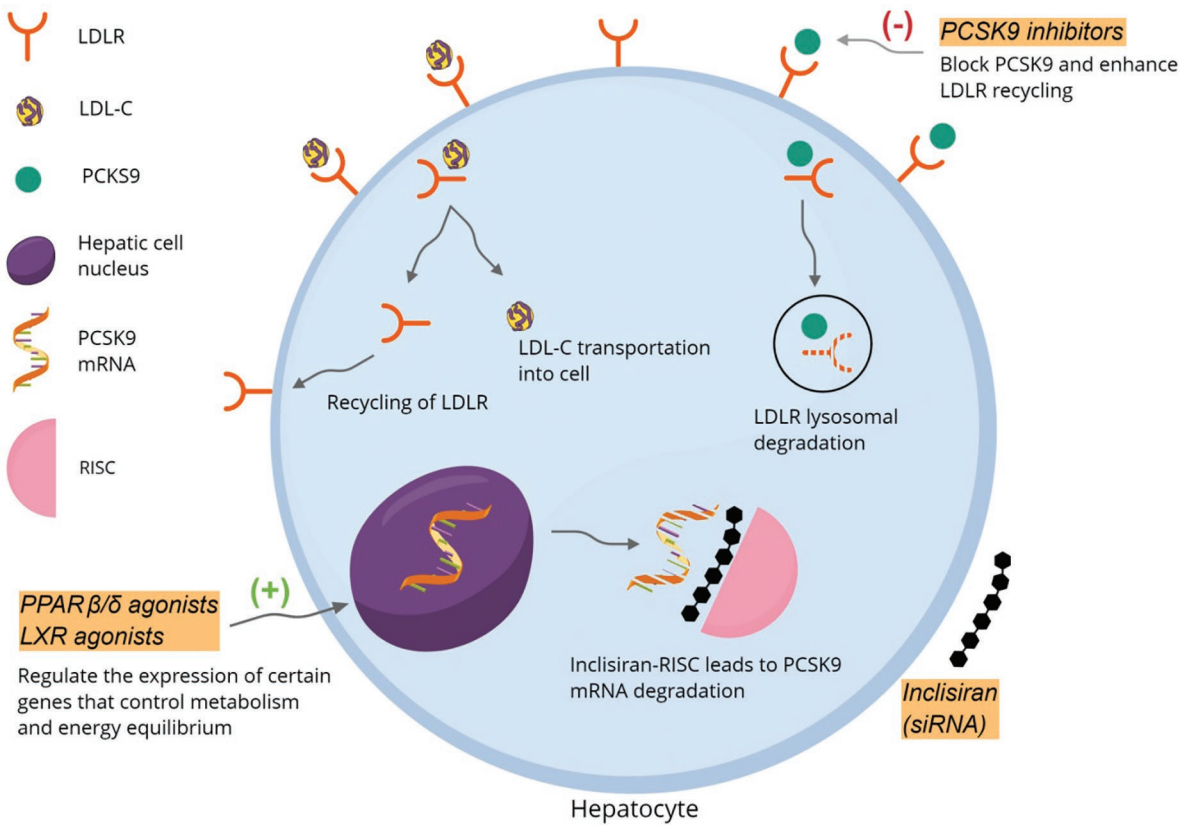
LXR agonists have been postulated to enhance reverse cholesterol transport and possibly inhibit intestinal cholesterol absorption. Therefore, LXR agonists may have the potential to inhibit the progression of atherosclerosis.[85] However, oral administration of LXR agonists to mice results in increased hepatic lipogenesis, including enhanced hepatic fatty acid synthesis and steatosis and increased secretion of triglyceride-rich VLDL leading to hypertriglyceridaemia.[84] In addition, LXR stimulation may cause elevation of LDL-C in species expressing cholesteryl ester transfer protein (CETP) such as non-human primates.[86]

LXRα is the predominant subtype, expressed primarily in the liver and appears to be responsible for observed increases in hepatic lipogenesis.[86] On the other hand, it has been demonstrated that selective LXRβ activation reverses atherosclerosis and cellular cholesterol overload in mice lacking LXRα and ApoE.[87]

WAY-252623 (LXR-623) is a highly selective and orally bioavailable synthetic LXR modulator that preferentially binds LXRβ *versus* LXRα. In an experimental study in non-human primates with normal lipid levels, WAY-252623 significantly decreased total cholesterol and LDL-C by 50–55% and 70–77%, respectively, in a time-dependent and dose-dependent manner. In addition, WAY-252623 enhanced the expression of the target genes *ABCA1/G1* in peripheral blood cells.[86] However, in a first-in-human, randomized, double-blind, placebo-controlled, inpatient, ascending-dose study, treatment with LXR-623 at the two highest doses tested caused central nervous system-related adverse events and thus further development of LXR-623 was abandoned.[79,85] Similar synthetic agonists, including CS-8080 and BMS-852927, have also been terminated due to safety concerns or other undisclosed reasons.[79,88,89]

On the other hand, BMS-779788, a partial LXRβ selective agonist, has been shown to decrease lipogenic potential and markedly improve plasma lipid profile as compared with a full

Figure 2. Mechanism of action of PCSK9 inhibitors, inclisiran, PPARβ/δ agonists and LXR agonists.



LDL-C, low-density lipoprotein cholesterol; LDLR, LDL receptors; LXR, liver X receptors; mRNA, messenger RNA; PCSK9, proprotein convertase subtilisin/kexin type 9; PPAR, peroxisome proliferator-activated receptors; RISC, RNA-induced silencing complexes; siRNA, small interfering RNA.

pan agonist in non-human primates, with similar potency in the induction of genes known to stimulate reverse cholesterol transport. These data support the concept of restricting LXRα activity to avoid the undesirable lipid effects of LXR agonists and thus improve LXR agonist therapeutic windows.[90]

Furthermore, another dual partial LXR agonist, IMB-808, also avoids common lipogenic side effects and has the potential of being used as a promising therapeutic agent for the prospective treatment of atherosclerosis in the future.[91] Notwithstanding, further large clinical studies are required to assess the potential benefits of LXR agonists in LDL-C lowering and the reduction of cardiovascular risk.

A summary of the results of the main trials discussed in this review is shown in Table 1. Brief illustrations of the mechanisms of the various drug classes described in this review are also provided (Figures 1–3).

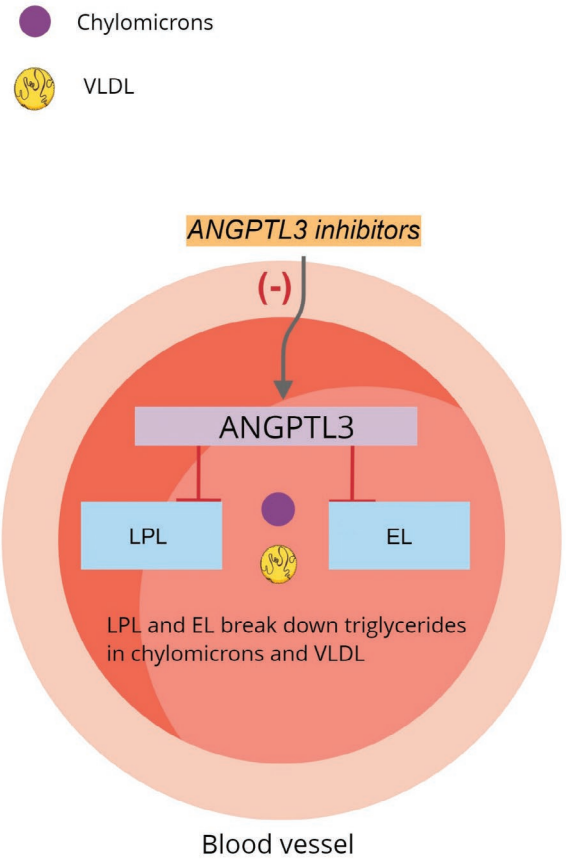
Cost-effectiveness of the novel LDL-C-lowering agents

The cost-effectiveness of the novel LDL-C-lowering agents represents a crucial factor that may determine access to these agents in clinical practice. The initial cost of PCSK9 inhibitors (US$14,100 per annum in the United States until October 2018) was very steep, far exceeding the costs of other lipid-lowering medications.[31,92] However, in October 2018 and February 2019, respectively, the main PCSK9 inhibitor manufacturing companies reduced the cost of PCSK9 inhibitors by 60%, to US$5850 per annum, thus greatly improving cost-effectiveness and making these agents more easily accessible in clinical practice.[31]

The Institute for Clinical and Economic Review (ICER) has recommended a health benefit price benchmark range for the annual price of bempedoic acid/ezetimibe in the general population of eligible patients from approximately US$1600 to US$2600, representing discounts from the wholesale acquisition cost of 36–60%.[93] The wholesale acquisition cost is an estimate of the manufacturer's list price for a drug to wholesalers or other direct purchasers, not including discounts or rebates.[94] The corresponding health benefit price benchmark range for the annual price of inclisiran in the general population of eligible patients is from US$3600 to US$6000.[93]

Regarding evinacumab, according to the manufacturing company, the average annual wholesale cost of the drug is

Figure 3. Mechanism of action of ANGPTL3 inhibitors.



ANGPTL3, angiopoietin-like protein 3; EL, endothelial lipase; LPL, lipoprotein lipase; VLDL, very low-density lipoprotein.

estimated to be US$450,000. This very high price tag certainly raises concerns about affordability and may have serious consequences for patient access. However, given the very limited treatment options for patients with HoFH and especially those with null–null variants and virtually absent LDLR activity, who may be successfully managed with evinacumab, the high price tag of the drug may not necessarily imply that evinacumab is overpriced in terms of cost-effectiveness.[95]

Conclusions

The role of LDL-C in the pathogenesis of atherosclerosis and CVD has been well recognized. Statins are the standard of care for the management of hypercholesterolaemia, and their effectiveness in lowering LDL-C and reducing CVD risk in both primary and secondary prevention has been well established. However, several patients fail to attain optimal LDL-C goals or are intolerant to statins, especially at high doses. Thus, extensive research has been focused on the development of alternative LDL-C-lowering therapies with a favourable side-effect profile, which (used alone or in combination with statins) would allow for effective and durable lowering of LDL-C levels and subsequent decrease in the risk of CVD.

PCSK9 inhibitors, bempedoic acid, inclisiran, ANGPTL3 inhibitors, PPARβ/δ agonists and LXR agonists are novel or upcoming LDL-C-lowering agents discussed in this article. Ongoing and future clinical studies will provide further invaluable information regarding the clinical efficacy of these agents and their role in the reduction of cardiovascular risk in patients with hypercholesterolaemia. Improvement in cost-effectiveness of the novel approved LDL-C-lowering agents may also facilitate access to these agents in clinical practice.

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