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Short Communication

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# Recent Advances and Emerging Therapies in the Management of Dyslipidemia

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## Abstract

*Dyslipidemia is a critical risk factor for atherosclerotic cardiovascular disease. Managing dyslipidemia through traditional lifestyle modifications is inadequate for many patients. Statins, the first-line pharmacological therapy, are effective, but are not always tolerated, do not target all types of dyslipidemia, and may not provide sufficient lipid lowering to achieve therapeutic objectives. Thus, novel therapeutic agents that are efficacious, safe, and well tolerated are warranted. This article provides a brief overview of several new and emerging therapies for the management of dyslipidemia including those targeting proprotein convertase subtilisin/kexin type 9, angiopoietin-like protein 3, apolipoprotein C-III, lipoprotein(a), adenosine triphosphate citrate lyase, and cholesteryl ester transfer protein (CETP), through traditional and new vehicle delivery systems, using recent advances in technology, i.e., monoclonal antibody and RNA interference. Growing evidence in support of the CETP inhibitor obicetrapib, an oral, once-daily investigational agent for managing dyslipidemia, suggests that it may be the first-in-class CETP inhibitor available for clinical use.*

**Keywords:** *Dyslipidemia; RNA interference technologies; monoclonal antibodies; CETP inhibitors; ACSVD*

## Commentary

Atherosclerotic cardiovascular disease (ASCVD) is one of the most clinically significant outcomes of dyslipidemia and is strongly linked to elevated concentrations of total cholesterol, low-density lipoprotein cholesterol (LDL-C), non-high-density lipoprotein cholesterol (non-HDL-C), apolipoprotein (apo) B, triglycerides (TG), and lipoprotein(a) (Lp[a]), and lower levels of HDL-C [1,2]. Management of dyslipidemia begins with modifying diet and physical activity, and mitigating secondary causes [1,2]. However, these interventions may not be adequate to reduce atherogenic lipoprotein lipid levels to meet therapeutic objectives. Statin therapy is the first-line pharmacological treatment for elevated LDL-C levels [1]. Although effective, statins may not be an option for those who are intolerant, and many patients, particularly those at elevated ASCVD risk, will require further lipid lowering beyond that which can be achieved with statin monotherapy [1,2]. In these cases, adjuncts to statins and alternative therapies are necessary. Recent advances have led to the development of several novel LDL-C-agents and numerous emerging therapies are on the horizon.

The introduction of the first proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitor biologics, evolocumab and alirocumab, in 2015 arguably marked the beginning of a new era of LDL-C-lowering medications that followed the relatively stagnant decades of lipid drug development since the initiation of statins in the late 1980s [3]. These are subcutaneously injected monoclonal antibodies targeting PCSK9, the enzyme that binds to LDL receptors stopping them from being recycled and decreasing removal of LDL from the blood. Evolocumab and alirocumab reduce LDL-C by up to ~60% and are indicated for preventing cardiovascular events and reducing LDL-C in primary hyperlipidemia and familial hypercholesterolemia (FH) as an adjunct to diet, alone or in combination with other lipid-lowering therapies [3]. Another recently approved human monoclonal antibody therapeutic, evinacumab, entered the marketplace in early 2021. It targets angiopoietin-like 3 (ANGPTL3), a protein that inhibits lipoprotein lipase and endothelial lipase thereby increasing TG and other lipids [4,5]. Evinacumab has been shown to reduce LDL-C by up to 49% and is indicated as an adjunct to other LDL-C lowering therapies for the treatment of adult and pediatric patients with homozygous FH [6]. It is administered by intravenous infusion.

RNA interference technologies are an integral component of the next generation of dyslipidemia therapies. These consist of small interfering RNAs (siRNAs) and RNase H-dependent antisense oligonucleotides (ASOs). siRNAs are double-stranded agents comprising an active "guide" strand complementary to target mRNA and a passenger strand to help stabilize the agent [7]. siRNAs are taken up by the cytosolic RNA-induced silencing complex (RISC), which ejects the passenger strand, leaving the guide strand to bind to the target mRNA and mediate its sequence-specific cleavage by the RISC RNase Argonaute 2 protein [7]. siRNA therapeutics will often contain a conjugate for tissue-specific targeting which decreases off-target effects and increases target potency.

Inclisiran is a first-in-class siRNA targeting PCSK9 initially approved by the Food and Drug Administration (FDA) in 2021 [8-10]. The siRNA in inclisiran is conjugated to triantennary N-acetylgalactosamine (GalNAc), targeting it to hepatic tissue [9]. Inclisiran is indicated as an adjunct to diet and maximally tolerated statin for the treatment of adults with heterozygous FH, clinical ASCVD, and patients at increased ASCVD risk who require additional LDL-C lowering; it is administered by subcutaneous injection. It has been shown to reduce LDL-C by up to ~52% vs. placebo [10], but its ability to reduce cardiovascular morbidity and mortality is still under investigation in a phase 3 cardiovascular outcome trial. Several other siRNA agents are in development, including ARO-APOC3 targeting apoC-III and olpasiran targeting Lp(a) [11-13].

ASOs are single-stranded oligonucleotides that bind to complementary sequences in target mRNAs and reduce gene expression by RNase H-mediated cleavage of the target RNA [7]. Volanesorsen and olezarsen are ASO-based therapies targeting apoC-III and pelacarsen is an ASO therapy targeting Lp(a) [13]. Volanesorsen is approved for use in the European Union, but due to safety concerns it is not approved by the U.S. FDA [13,14]; phase 3 clinical trials of olezarsen and pelacarsen are underway [13].

While injectable agents represent a large portion of the most recently approved and emerging dyslipidemia therapies, oral agents continue to be preferred by many patients, and advances in small molecule "pills" with novel targets should not be overlooked. Bempedoic acid is a small molecule therapeutic that inhibits adenosine triphosphate (ATP) citrate lyase, an enzyme upstream of the enzyme targeted by statins, 3-hydroxy-3-methylglutaryl coenzyme A reductase [13,15]. Unlike statins, bempedoic acid is a prodrug that is only converted to the active drug in the liver, and not muscles. As a result, it might be preferable for patients with muscle-related complaints while taking statins [13,15]. Bempedoic acid was approved by the FDA in 2020 as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous FH or established ASCVD who require additional LDL-C lowering. Bempedoic acid resulted in an ~20% reduction in LDL-C and reduced the risk of major adverse cardiovascular events (MACE) by 13% among "statin-intolerant" patients with or at high risk for ASCVD [15]. Another oral medication in phase 2 development is MK-0616, an experimental macrocyclic peptide PCSK9 inhibitor, that reduced LDL-C by ~61% vs. placebo among subjects with a range of ASCVD risk [16].

Another promising oral agent which has reached phase 3 clinical trial development is obicetrapib, a novel selective cholesteryl ester transfer protein (CETP) inhibitor. CETP is mainly located in the liver and adipose tissue and is involved in the transfer of cholesteryl esters from HDL to very low-density lipoproteins, intermediate-density lipoproteins, and LDL in exchange for TG [17]. CETP has been a target for dyslipidemia therapy since patients with genetic CETP deficiency and extremely elevated levels of HDL-C and lower risk of coronary heart disease were first identified in Japan in the 1980s [18]. However, the development of the four CETP inhibitors prior to obicetrapib was abandoned for a variety of reasons [19]. Torcetrapib had significantly increased rates of cardiovascular events and mortality due to off-target effects, and phase 3 cardiovascular outcomes trials of both dalcetrapib and evacetrapib were terminated early due to lack of efficacy [19]. While anacetrapib significantly reduced LDL-C and apoB by 17% and 18%, respectively, and reduced coronary events by 9% in a phase 3 trial of more than 30,000 patients, it is a highly lipophilic compound that accumulates in adipose, and its development was also discontinued [20,21]. It is now understood that the potential ASCVD risk reducing mechanism of CETP inhibitors relates to their effects on apoB-containing lipoproteins and not their ability to raise HDL-C [17].

Despite the turbulent history of pharmacologic CETP inhibitors, CETP inhibition continues to be an attractive target, particularly considering the results from studies of obicetrapib [17,19, 22-24]. Obicetrapib reduces CETP activity to a greater extent than its predecessors at equal or lesser doses, and has a less lipophilic chemical structure [17,22]. Phase 1 and 2 trials have demonstrated the safety and lipoprotein lipid-altering efficacy of obicetrapib as monotherapy, in conjunction with statins, on top of high-intensity statins, and with ezetimibe on top of high-intensity statins [22-24]. Most recently the results from the Randomized Study of Obicetrapib as an Adjunct to Statin Therapy (ROSE) [23], and the Study to Evaluate the Effect of Obicetrapib in Combination with Ezetimibe as an Adjunct to High-Intensity Statin Therapy (ROSE2) were published [24]. In ROSE, patients with LDL-C ≥70 mg/dL received 5 or 10 mg/d of obicetrapib or placebo added to high-intensity statin for 12 weeks. LDL-C was decreased by up to 50.8%, apoB by up to 29.8%, non-HDL-C by up to 44.4%, and Lp(a) by up to 56.5%, and HDL-C was increased by up to 165% with obicetrapib compared to placebo [23]. In ROSE2, patients with LDL-C >70 mg/dL and TG <400 mg/dL on stable, high-intensity

statin received daily doses of 10 mg obicetrapib monotherapy, 10 mg obicetrapib plus 10 mg ezetimibe in combination, or placebo for 12 weeks [24]. Compared with placebo, the combination and obicetrapib monotherapy treatments, respectively, reduced LDL-C by 63.4% and 43.5%, apoB by 34.4% and 24.2%, and non-HDL-C by 55.6% and 37.5%, and raised HDL-C by 136% and 142% [24].

Three pivotal phase 3 registration trials of obicetrapib are underway including the Randomized Study to Evaluate the Effect of Obicetrapib on Top of Maximum Tolerated Lipid-Modifying Therapies (BROADWAY), the Evaluate the Effect of Obicetrapib in Patients with Heterozygous Familial Hypercholesterolemia on Top of Maximum Tolerated Lipid-Modifying Therapies (BROOKLYN) trial, and the Cardiovascular Outcome Study to Evaluate the Effect of Obicetrapib in Patients with Cardiovascular Disease (PREVAIL). PREVAIL is enrolling 9000 patients with a history of ASCVD and inadequately controlled LDL-C, despite being on maximally tolerated lipid-modifying therapies, to receive placebo or 10 mg obicetrapib once daily to assess its effect on the incidence of MACE. Results from BROADWAY and BROOKLYN are expected in 2024, and those from PREVAIL in 2026. Among the several thousand patients enrolled in phase 1, 2, and (to-date) 3 clinical trials, obicetrapib has demonstrated a favorable safety profile [17, 22-24].

## Conclusion

Decades after the introduction of statins, a new wave of dyslipidemia targeting therapeutics has emerged. These recently approved and emerging therapies have new biological targets, i.e., evolocumab, alirocumab, and inclisiran target PCSK9; evinacumab targets ANGPTL3; ARO-APOC3, volanesorsen, and olezarsen target apoC-III; olpasiran and pelacarsen target Lp(a); bempedoic acid targets ATP acyl transferase; and obicetrapib targets CETP. Several also utilize new technologies of monoclonal antibodies and RNA interference, and new routes of administration, including subcutaneous injections and intravenous infusions. Obicetrapib is a low-dose, once daily, oral, next generation CETP inhibitor, which has shown significant promise for the management of dyslipidemia in phase 1, 2, and ongoing phase 3 clinical trials and is expected to be the first-in-class CETP inhibitor for clinical use.

## Conflict of Interest Statement

Authors declare to have no conflict of interest relevant to this article.

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