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Review Article

Oral PCSK9 Inhibitors: Current Evidence, Clinical Applications And Future Perspectives In Lipid-Lowering Therapy

Fahim Zakariya*[1], Sajitha G[2]

[1]*Department of Pharmacy Practice, College of Pharmaceutical Sciences, Govt Medical College TVM, Kerala, India*
[2]*Department of Pharmacy Practice, College of Pharmaceutical Sciences, Govt Medical College TVM, Kerala, India*

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ABSTRACT

Hypercholesterolemia remains a major modifiable risk factor for atherosclerotic cardiovascular disease (ASCVD), despite the availability of effective lipid-lowering therapies. Although statins remain the cornerstone of treatment, many patients fail to achieve recommended low-density lipoprotein cholesterol (LDL-C) targets or are unable to tolerate intensive lipid-lowering therapy. Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors have significantly improved lipid management by providing substantial reductions in LDL-C and cardiovascular risk. However, the requirement for subcutaneous administration has limited their widespread acceptance and long-term adherence. The development of oral PCSK9 inhibitors represents a significant advancement in lipid-lowering therapy by combining potent LDL-C reduction with the convenience of oral administration. This narrative review summarizes the biological role of PCSK9, the limitations of current lipid-lowering therapies, and the development of emerging oral PCSK9 inhibitors, including enlicitide, AZD0780, DC371739, CVI-LM001, and other investigational agents. Available clinical evidence demonstrates that oral PCSK9 inhibitors, particularly enlicitide, produce substantial reductions in LDL-C, non-HDL cholesterol, apolipoprotein B, and lipoprotein(a) while maintaining a favorable safety profile in clinical trials. The review also discusses the advantages and current challenges associated with oral PCSK9 inhibitors, including the need for long-term cardiovascular outcome data, cost-effectiveness analyses, and real-world evidence. Furthermore, ongoing Phase III trials, personalized treatment strategies, combination therapy, and advances in oral peptide drug delivery are expected to shape the future of this therapeutic class. Overall, oral PCSK9 inhibitors have the potential to expand treatment options for patients with hypercholesterolemia by improving treatment accessibility, patient acceptance, and adherence. The recent approval of enlicitide marks an important milestone in oral lipid-lowering therapy, while continued development of other oral PCSK9 inhibitors

***Corresponding Author:** Fahim Zakariya
Address: *Department of Pharmacy Practice, College of Pharmaceutical Sciences, Govt Medical College TVM, Kerala, India*
Email ✉: fahimzakariya60@gmail.com

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is expected to further expand treatment options

INTRODUCTION

Cardiovascular disease (CVD) remains the leading cause of mortality worldwide and is responsible for a substantial burden of morbidity and healthcare expenditure. Elevated low-density lipoprotein cholesterol (LDL-C) is a well-established and modifiable risk factor for the development of atherosclerotic cardiovascular disease (ASCVD). Numerous clinical trials have consistently demonstrated that lowering LDL-C significantly reduces the risk of myocardial infarction, stroke, and cardiovascular death. Consequently, current international guidelines recommend intensive LDL-C reduction, particularly in patients at high and very high cardiovascular risk, to improve long-term cardiovascular outcomes. (1)

Statins remain the cornerstone of lipid-lowering therapy because of their proven efficacy in reducing LDL-C levels and cardiovascular events. However, despite maximally tolerated statin therapy, many patients fail to achieve recommended LDL-C targets. Factors such as statin intolerance, familial hypercholesterolemia, poor adherence, and inadequate lipid control necessitate the use of additional lipid-lowering agents. Non-statin therapies, including ezetimibe, bempedoic acid, PCSK9 monoclonal antibodies, and small interfering RNA (siRNA)-based therapies such as inclisiran, have expanded the available treatment options and improved lipid management in high-risk patients. (2)

Proprotein convertase subtilisin/kexin type 9 (PCSK9) plays a crucial role in cholesterol homeostasis by promoting the degradation of hepatic LDL receptors, thereby reducing the clearance of circulating LDL-C. Pharmacological inhibition of PCSK9 increases the number of available LDL receptors on hepatocytes, resulting in enhanced LDL-C clearance and substantial reductions in plasma LDL-C concentrations. Injectable PCSK9 inhibitors, including evolocumab and alirocumab, together with the siRNA therapy inclisiran, have demonstrated remarkable efficacy in lowering LDL-C and reducing cardiovascular risk. Nevertheless, their widespread use is limited by factors such as subcutaneous administration, treatment cost, and patient preference for oral medications. These limitations have encouraged the development of orally administered PCSK9 inhibitors that may provide comparable efficacy with improved convenience and treatment adherence. (3)

Recent advances in drug development have led to the emergence of several oral PCSK9 inhibitors, including enlicitide (MK-0616), AZD0780, DC371739, CVI-LM001, and other investigational molecules. Early clinical studies have demonstrated promising LDL-C reductions with favorable safety profiles, while recent phase 2 and phase 3 trials have further highlighted the therapeutic potential of these agents. Oral PCSK9 inhibitors may overcome important barriers associated with injectable therapies and could represent a significant advancement in the management of hypercholesterolemia and cardiovascular risk. (1–3)

Therefore, this narrative review aims to summarize the biological role of PCSK9 in lipid metabolism, discuss the limitations of currently available lipid-lowering therapies, review the emerging evidence on oral PCSK9 inhibitors, and highlight their potential role in the future management of hypercholesterolemia and ASCVD.

BIOLOGY OF PCSK9

Discovery:

Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a serine protease that plays a central role in cholesterol metabolism by regulating the number of low-density lipoprotein receptors (LDLRs) on the surface of hepatocytes. PCSK9 was first identified in 2003 by Abifadel and colleagues, who demonstrated that gain-of-function mutations in the PCSK9 gene cause autosomal dominant hypercholesterolemia. This landmark discovery established PCSK9 as the third major genetic determinant of familial hypercholesterolemia after mutations in the LDLR and APOB genes. Since then, PCSK9 has emerged as one of the most important therapeutic targets for lowering low-density lipoprotein cholesterol (LDL-C) and reducing cardiovascular risk.

Further evidence supporting the importance of PCSK9 came from the study by Cohen et al., which showed that individuals carrying naturally occurring loss-of-function variants in the PCSK9 gene had significantly lower LDL-C levels and a markedly reduced lifetime risk of coronary heart disease. These findings provided compelling genetic evidence that inhibition of PCSK9 could produce substantial cardiovascular benefits while maintaining a favorable safety profile. (4)

Structure:

The human PCSK9 gene is located on chromosome 1p32.3 and encodes a protein consisting of 692 amino acids. PCSK9 is synthesized primarily in the liver, although lower levels of expression have also been reported in the intestine, kidney, and central nervous system. The protein is initially produced as an inactive precursor (zymogen), which undergoes autocatalytic cleavage in the endoplasmic reticulum to generate its mature form before being secreted into the circulation. The prodomain remains attached to the mature protein and acts as a molecular chaperone, facilitating proper folding and secretion while preventing further enzymatic activity(5).

Structurally, mature PCSK9 consists of three major domains: the N-terminal prodomain, the catalytic domain, and the C-terminal cysteine-rich domain. Although classified as a serine protease, PCSK9 exerts its biological effects primarily through protein–protein interactions rather than enzymatic cleavage of its target proteins. Structural studies have demonstrated that proper folding, autocatalytic processing, and secretion are essential for normal PCSK9 function, and mutations affecting these processes can significantly alter plasma LDL-C concentrations.(5)

Biosynthesis and Regulation:

PCSK9 expression is tightly regulated by intracellular cholesterol homeostasis. Reduced intracellular cholesterol activates sterol regulatory element-binding protein-2 (SREBP-2), a transcription factor that simultaneously increases the expression of both the LDL receptor and PCSK9. Consequently, lipid-lowering therapies such as statins increase hepatic PCSK9 expression while upregulating LDL receptors. This compensatory increase in PCSK9 limits the cholesterol-lowering efficacy of statins by promoting LDL receptor degradation, providing the biological rationale for combining statins with PCSK9-targeted therapies.

After synthesis, PCSK9 undergoes autocatalytic cleavage within the endoplasmic reticulum. This processing step is essential because only mature, secreted PCSK9 can interact effectively with LDL receptors. Mutations that impair protein folding or secretion reduce PCSK9 activity and are associated with lower plasma LDL-C concentrations. Conversely, gain-of-function mutations enhance LDL receptor degradation,

leading to elevated LDL-C levels and increased cardiovascular risk. (5)

PCSK9–LDL Receptor Interaction:

The principal physiological function of PCSK9 is to regulate the recycling of LDL receptors. Under normal conditions, circulating LDL particles bind to LDL receptors on hepatocytes and are internalized through receptor-mediated endocytosis. Within the acidic environment of the endosome, LDL particles dissociate from the receptor, allowing the receptor to recycle back to the cell surface for repeated rounds of LDL clearance.(6)

When circulating PCSK9 binds to the epidermal growth factor-like repeat A (EGF-A) domain of the LDL receptor, the receptor–PCSK9 complex is internalized together. Unlike the normal recycling pathway, PCSK9 directs the receptor toward lysosomal degradation instead of recycling. As a result, fewer LDL receptors return to the hepatocyte surface, reducing hepatic LDL clearance and increasing circulating LDL-C concentrations. This mechanism explains why increased PCSK9 activity is associated with hypercholesterolemia, whereas inhibition of PCSK9 enhances LDL receptor availability and promotes LDL-C removal from the bloodstream.(5)

Clinical Significance:

The discovery of PCSK9 transformed the understanding of lipid metabolism and cardiovascular disease. Genetic studies have consistently demonstrated that gain-of-function mutations increase plasma LDL-C levels and predispose individuals to familial hypercholesterolemia, whereas loss-of-function mutations produce lifelong reductions in LDL-C and substantially lower the risk of atherosclerotic cardiovascular disease. In the landmark study by Cohen et al., individuals carrying loss-of-function PCSK9 variants experienced reductions in LDL-C together with a significantly lower incidence of coronary heart disease, highlighting the long-term cardiovascular benefits of reduced PCSK9 activity. (4)

These observations established PCSK9 as an attractive therapeutic target for lipid lowering. Several pharmacological approaches have subsequently been developed to inhibit PCSK9, including monoclonal antibodies, small interfering RNA (siRNA), vaccines, gene-editing technologies, and more recently, orally active small-molecule inhibitors. Among these, oral PCSK9 inhibitors represent a promising advance because they may overcome many of the limitations associated with injectable therapies, including issues related to patient acceptance, treatment adherence, and accessibility. Their development marks a significant step toward more convenient and potentially broader implementation of PCSK9-targeted lipid-lowering therapy.(7)

CURRENT LIPID-LOWERING THERAPIES

Reducing low-density lipoprotein cholesterol (LDL-C) remains the cornerstone of preventing and managing atherosclerotic cardiovascular disease (ASCVD). Over the past three decades, several lipid-lowering therapies have been developed that target different steps in cholesterol metabolism. Although statins remain the first-line treatment, many patients fail to achieve recommended LDL-C targets because of inadequate response, intolerance, or poor adherence. Consequently, additional therapeutic strategies, including ezetimibe, bempedoic acid, and PCSK9-targeted therapies, have been introduced to provide further LDL-C reduction and improve cardiovascular outcomes.(6)

Statins:

Statins are competitive inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme in hepatic cholesterol biosynthesis. By reducing intracellular cholesterol synthesis, statins activate sterol regulatory element-binding protein-2 (SREBP-2), leading to increased expression of hepatic LDL receptors (LDLRs) and enhanced clearance of circulating LDL-C.(8)

Large randomized clinical trials have consistently demonstrated that statins reduce LDL-C by approximately 30–55%, depending on the agent and dose, while significantly lowering the risk of myocardial infarction, stroke, and cardiovascular mortality. Consequently, statins remain the first-line therapy in current international dyslipidemia guidelines.

Despite their proven efficacy, statins have several limitations. Statin-associated muscle symptoms, elevated liver enzymes, and perceived intolerance contribute to poor adherence in some patients. Furthermore, activation of SREBP-2 simultaneously increases PCSK9 expression, partially offsetting LDLR upregulation and limiting the maximal LDL-C reduction achievable with statin monotherapy. This compensatory increase in PCSK9 provides a strong biological rationale for combining statins with PCSK9-targeted therapies.

Ezetimibe:

Ezetimibe selectively inhibits Niemann–Pick C1-like 1 (NPC1L1), the cholesterol transporter located in the brush border of the small intestine. By reducing intestinal cholesterol absorption, ezetimibe decreases hepatic cholesterol stores and promotes LDLR expression, thereby enhancing plasma LDL-C clearance.

As monotherapy, ezetimibe lowers LDL-C by approximately 15–25%. When added to statin therapy, it provides additional LDL-C reduction and has demonstrated improved cardiovascular outcomes, particularly in patients with recent acute coronary syndrome. Owing to its favorable safety profile, oral administration, and low cost, ezetimibe is commonly recommended as the second-line agent when LDL-C goals are not achieved with maximally tolerated statins(8,9)

Bempedoic Acid:

Bempedoic acid is a first-in-class inhibitor of adenosine triphosphate (ATP)-citrate lyase (ACL), an enzyme located upstream of HMG-CoA reductase in the cholesterol biosynthetic pathway. Unlike statins, bempedoic acid is activated primarily in the liver and not in skeletal muscle, reducing the likelihood of muscle-related adverse effects.

Clinical studies have shown that bempedoic acid lowers LDL-C by approximately 15–25% as monotherapy and provides greater reductions when combined with ezetimibe or statins. The CLEAR Outcomes trial further demonstrated cardiovascular risk reduction in statin-intolerant patients, supporting its role as an effective oral alternative for individuals unable to tolerate high-intensity statin therapy.(9)

PCSK9-Targeted Therapies

The discovery of proprotein convertase subtilisin/kexin type 9 (PCSK9) transformed lipid management by introducing therapies that directly preserve LDLR recycling. PCSK9 binds to LDLRs on hepatocytes and directs them toward lysosomal degradation rather than recycling to the cell surface. Consequently, elevated PCSK9 activity reduces hepatic LDLR availability, resulting in increased circulating LDL-C. Inhibition of PCSK9 prevents LDLR degradation, increases receptor

recycling, and markedly enhances LDL-C clearance.

Currently approved PCSK9-targeted therapies include monoclonal antibodies (evolocumab, alirocumab, and tafolecimab) and the small interfering RNA (siRNA) inclisiran. Monoclonal antibodies neutralize circulating PCSK9, whereas inclisiran suppresses hepatic PCSK9 synthesis through RNA interference. These agents typically reduce LDL-C by approximately 50–60% and have demonstrated significant reductions in major adverse cardiovascular events in high-risk patients.

Despite their excellent efficacy, injectable PCSK9 inhibitors remain underutilized due to several practical limitations, including high treatment costs, subcutaneous administration, cold-chain storage, and patient reluctance toward lifelong injections. These challenges have stimulated considerable interest in developing orally administered PCSK9 inhibitors that combine the potent LDL-C lowering efficacy of PCSK9 inhibition with the convenience of oral therapy.(10,11)

Table 1:

Drug class	Representative drugs	Mechanism of action	Approximate LDL-C reduction	Route
Statins	Atorvastatin, Rosuvastatin	Inhibit HMG-CoA reductase, increasing hepatic LDL receptor expression	30–55%	Oral
Cholesterol absorption inhibitor	Ezetimibe	Inhibits NPC1L1-mediated intestinal cholesterol absorption	15–25%	Oral
ATP-citrate lyase inhibitor	Bempedoic acid	Inhibits ATP-citrate lyase, reducing hepatic cholesterol synthesis	15–25%	Oral
PCSK9 monoclonal antibodies	Evolocumab, Alirocumab, Tafolecimab	Neutralize circulating PCSK9 and prevent LDLR degradation	50–60%	Subcutaneous injection
PCSK9 siRNA	Inclisiran	Silences hepatic PCSK9 mRNA, reducing PCSK9 synthesis	~50%	Subcutaneous injection (every 6 months)

Oral PCSK9 inhibitors*	Enlicitide (MK-0616	Small molecules or macrocyclic peptides that inhibit PCSK9 function	Approved (≈55–60%)	Oral

ORAL PCSK9 INHIBITORS

Why Oral PCSK9 Inhibitors?

PCSK9-targeted therapies have significantly improved the treatment of hypercholesterolemia, particularly in patients who do not achieve recommended low-density lipoprotein cholesterol (LDL-C) targets despite maximally tolerated statin therapy. Injectable PCSK9 monoclonal antibodies, such as evolocumab and alirocumab, reduce LDL-C by approximately 60%, while inclisiran, a small interfering RNA (siRNA), produces sustained LDL-C reductions of around 50%. These therapies have demonstrated substantial cardiovascular benefits and are widely recommended for high-risk patients. (3)

Despite their effectiveness, injectable PCSK9 inhibitors have limitations, including the need for regular subcutaneous administration, high treatment costs, and reduced patient acceptance, all of which may affect long-term adherence and accessibility. These challenges have driven the search for effective oral alternatives that provide comparable lipid-lowering efficacy with greater convenience.(3)

Oral PCSK9 inhibitors have emerged as a promising approach to overcome these limitations. Designed for once-daily administration, these agents offer improved convenience and can be readily combined with established lipid-lowering therapies such as statins, ezetimibe, and bempedoic acid. Several investigational agents, including enlicitide decanoate (MK-0616), AZD0780, DC371739, CVI-LM001, and NNC0385-0434, have demonstrated encouraging lipid-lowering efficacy and favorable safety profiles in early clinical studies.

Overall, oral PCSK9 inhibitors represent an important advancement in lipid-lowering therapy by combining the efficacy of PCSK9 inhibition with the convenience of oral administration. If ongoing clinical trials continue to confirm their efficacy and safety, these agents have expanded treatment options following the approval of enlicitide, while additional oral agents continue clinical development.

Development of Oral PCSK9 Inhibitors:

The identification of PCSK9 as a key regulator of low-density lipoprotein receptor (LDLR) degradation established it as an important therapeutic target for lowering LDL cholesterol (LDL-C). Initial therapeutic approaches focused on injectable agents, including monoclonal antibodies (evolocumab and alirocumab) and the small interfering RNA (siRNA) inclisiran, which demonstrated substantial LDL-C reduction and cardiovascular benefits. However, their dependence on subcutaneous administration and high cost highlighted the need for more convenient treatment options. (2)

Developing oral PCSK9 inhibitors was particularly challenging because PCSK9 interacts with the LDL receptor through a relatively flat protein–protein interface, making it difficult for conventional small molecules to disrupt this interaction. Advances in medicinal chemistry have since enabled the development of oral agents

employing different mechanisms, including direct inhibition of the PCSK9–LDLR interaction and suppression of PCSK9 gene transcription.

Several oral PCSK9 inhibitors are currently under clinical development. Enlicitide decanoate (MK-0616), AZD0780, and NNC0385-0434 directly block the interaction between PCSK9 and the LDL receptor, whereas DC371739 and CVI-LM001 reduce PCSK9 expression through transcriptional inhibition. Most of these agents are designed for once-daily oral administration and have demonstrated encouraging lipid-lowering efficacy and favorable safety profiles in early clinical studies. Among them, Enlicitide became the first approved oral PCSK9 inhibitor following successful Phase III clinical trials, representing a major milestone in PCSK9-targeted therapy(12)

Enlicitide (MK-0616):

Enlicitide decanoate (MK-0616) is the first approved oral PCSK9 inhibitor for the treatment of hypercholesterolemia. It is a macrocyclic peptide designed to bind circulating PCSK9 and prevent its interaction with the low-density lipoprotein receptor (LDLR). By blocking this interaction, enlicitide preserves LDLR recycling on hepatocytes, thereby enhancing hepatic clearance of LDL-C from the circulation. Unlike injectable monoclonal antibodies, enlicitide is administered orally once daily, offering a more convenient treatment option for patients requiring intensive lipid-lowering therapy.

Pharmacokinetic studies demonstrated that enlicitide has favorable oral bioavailability when administered with a permeation enhancer. Early clinical studies showed dose-dependent reductions in circulating free PCSK9 and LDL-C with good tolerability, supporting its progression through clinical development.

Phase II and Phase III clinical trials demonstrated significant dose-dependent reductions in LDL-C. The CORALreef trial further confirmed its efficacy in patients receiving background lipid-lowering therapy, with LDL-C reductions exceeding 50%, accompanied by reductions in apolipoprotein B and lipoprotein(a). The incidence of adverse events was comparable to placebo, and most treatment-related events were mild, indicating a favorable safety profile.

Following the successful completion of clinical trials, enlicitide became the first approved oral PCSK9 inhibitor, representing a major milestone in lipid-lowering therapy. Its combination of potent LDL-C reduction, once-daily oral administration, and favorable safety profile provides an effective oral alternative to injectable PCSK9-targeted therapies and expands the therapeutic options for patients with hypercholesterolemia

AZD0780:

AZD0780 is a first-in-class oral small-molecule PCSK9 inhibitor developed for patients whose LDL-C levels remain inadequately controlled despite statin therapy. Unlike transcriptional inhibitors, AZD0780 directly binds to circulating PCSK9 and prevents its interaction with the LDL receptor, thereby increasing LDL receptor recycling and enhancing LDL-C clearance.

In Phase I clinical studies, AZD0780 administered at doses of 30 mg or 60 mg daily demonstrated good safety, tolerability, and pharmacokinetic properties. When combined with rosuvastatin, treatment resulted in an additional 52% reduction in LDL-C, with an overall LDL-C reduction of approximately 78% from baseline**.** No serious adverse events were reported, and the drug was generally well tolerated, supporting its advancement into Phase II clinical trials.

Subsequent clinical studies have further confirmed the lipid-lowering efficacy of AZD0780, making it one of the most promising oral PCSK9 inhibitors currently under development.

DC371739:

DC371739 is an investigational oral PCSK9 inhibitor with a unique mechanism of action. Rather than directly binding circulating PCSK9, it suppresses the transcription of both PCSK9 and angiopoietin-like protein 3 (ANGPTL3) by inhibiting the binding of hepatocyte nuclear factor-1α (HNF-1α) to their promoter regions. This dual mechanism may contribute to improvements in both cholesterol and triglyceride metabolism.

Phase I clinical studies demonstrated favorable pharmacokinetic properties, with a half-life of approximately 23–26 hours, supporting once-daily dosing. Treatment with 40 mg daily for 28 days significantly reduced LDL-C by 19%, while triglycerides and apolipoprotein B were reduced by 27% and 25%, respectively. The drug was well tolerated, with no major safety concerns reported, and is currently undergoing Phase Ib/IIa clinical evaluation.

CVI-LM001:

CVI-LM001 is another investigational oral PCSK9 inhibitor that reduces PCSK9 expression through transcriptional inhibition while also activating AMP-activated protein kinase (AMPK), which may provide additional metabolic benefits. This dual mechanism differentiates CVI-LM001 from other oral PCSK9 inhibitors currently in development.

Clinical studies have demonstrated rapid oral absorption and favorable pharmacokinetic characteristics suitable for once-daily administration. In Phase Ib studies, treatment with 300 mg daily for 28 days reduced LDL-C by 26.3%, total cholesterol by 20.1%, apolipoprotein B by 17.4%, and circulating PCSK9 by 39.2%. CVI-LM001 was generally well tolerated in both healthy volunteers and patients with hypercholesterolemia, supporting its continued clinical development.

Other Emerging Oral PCSK9 Inhibitors:

Several additional oral PCSK9 inhibitors are currently being investigated to improve lipid-lowering therapy. Among these, NNC0385-0434 is a peptide that mimics the epidermal growth factor-like repeat A (EGF-A) domain of the LDL receptor and inhibits the interaction between PCSK9 and LDLR. Clinical studies demonstrated LDL-C reductions approaching **60%**, along with reductions in lipoprotein(a). However, despite encouraging efficacy and acceptable safety, its clinical development was discontinued because of portfolio considerations rather than safety concerns.

Overall, currently available oral PCSK9 inhibitors employ two major strategies: direct inhibition of the PCSK9–LDLR interaction (enlicitide, AZD0780, and NNC0385-0434) or suppression of PCSK9 expression (DC371739 and CVI-LM001). Most agents have demonstrated favorable pharmacokinetic profiles with once-daily dosing and encouraging lipid-lowering efficacy in early clinical trials. Although long-term cardiovascular outcome data are still awaited, these agents represent promising additions to future lipid-lowering therapy.

Table 2: Characteristics of Oral PCSK9 Inhibitors

Drug	Company	Mechanism of action	Approximate LDL-C reduction	Current Status

Enlicitide (MK-0616	Merck	Macrocyclic peptide; inhibits PCSK9-LDLR interaction	>50–60%	Approved
AZD0780	AstraZeneca	Small-molecule inhibitor that binds circulating PCSK9	~52%	Ongoing clinical development
DC371739	Dizal	Inhibits PCSK9 and ANGPTL3 transcription	~19%	Early clinical development
CVI-LM001	CSPC Pharmaceutical	Inhibits PCSK9 transcription and activates AMPK	~26%	Clinical development

CLINICAL EVIDENCE

Major Clinical Trials:

Clinical evaluation of oral PCSK9 inhibitors has primarily focused on enlicitide (MK-0616), with additional evidence emerging for agents such as AZD0780 (laroprovstat) and NNC0385-0434. Early phase clinical studies demonstrated that MK-0616 is orally bioavailable, effectively inhibits circulating PCSK9, and produces clinically meaningful reductions in LDL-C when administered once daily. In a Phase I study involving healthy volunteers and statin-treated patients, MK-0616 reduced free circulating PCSK9 by more than 90% and achieved LDL-C reductions of approximately 58–61% after 14 days of treatment, while maintaining a favorable safety profile. (13)

Subsequent Phase II and Phase III trials further confirmed these findings. The CORALreef and CORALreef-HeFH studies demonstrated that once-daily enlicitide, administered in combination with background lipid-lowering therapy, consistently reduced LDL-C by approximately 60% in patients with hypercholesterolemia, including those with heterozygous familial hypercholesterolemia. Similar lipid-lowering efficacy has also been reported with other oral PCSK9 inhibitors under clinical development, including AZD0780 (laroprovstat) and NNC0385-0434, indicating that oral inhibition of PCSK9 is a reproducible therapeutic strategy across different molecular platforms. (14)

Comparative Efficacy:

Current evidence suggests that oral PCSK9 inhibitors achieve LDL-C reductions comparable to currently approved injectable PCSK9 therapies. A recent meta-analysis of five randomized controlled trials involving 3,295 participants reported an overall LDL-C reduction of **59.3%** compared with placebo. In addition to LDL-C lowering, oral PCSK9 inhibitors significantly reduced apolipoprotein B (−49.5%), non-HDL cholesterol (−55.4%), and lipoprotein(a)

(−22.7%), demonstrating broad improvement in atherogenic lipid profiles. (14)

Notably, the lipid-lowering efficacy of oral agents appears comparable to that achieved with injectable monoclonal antibodies such as evolocumab and alirocumab, as well as inclisiran. The availability of an effective oral formulation may improve treatment acceptance, adherence, and accessibility while maintaining potent LDL-C reduction, potentially expanding the use of PCSK9-targeted therapy in routine clinical practice. (15)

Safety:

Available clinical data indicate that oral PCSK9 inhibitors are generally well tolerated. In Phase 1 and multiple-dose studies of MK-0616, no serious safety concerns or dose-limiting toxicities were identified, and most adverse events were mild to moderate in severity. Commonly reported events included dyspepsia, gastroesophageal reflux, dry mouth, dizziness, and headache, with frequencies similar to placebo. No clinically meaningful changes in laboratory parameters, vital signs, or electrocardiographic findings were observed. (16)

The favorable safety profile has been supported by pooled evidence from randomized controlled trials. In the recent meta-analysis, oral PCSK9 inhibitors did not increase the risk of serious adverse events compared with placebo (risk ratio 0.84; 95% CI 0.68–1.03). These findings suggest that oral PCSK9 inhibitors provide potent lipid lowering with good short-term tolerability, although longer-duration studies and cardiovascular outcome trials are required to establish their long-term safety and clinical benefits.(17)

ADVANTAGES AND CHALLENGES OF ORAL PCSK9 INHIBITORS

Advantages:

Oral PCSK9 inhibitors represent a significant advancement in lipid-lowering therapy by addressing several limitations associated with currently available injectable PCSK9-targeted agents. The most notable advantage is the convenience of oral administration, which has the potential to improve patient acceptance and long-term adherence, particularly among individuals who are reluctant to receive regular subcutaneous injections. Because dyslipidemia requires lifelong treatment, an oral formulation may facilitate sustained therapy and improve persistence in clinical practice. Injectable therapies are frequently associated with poor treatment persistence owing to injection-related concerns, high out-of-pocket costs, and complex reimbursement procedures, highlighting the need for more patient-friendly alternatives. (18,19)

Among oral candidates, enlicitide has demonstrated LDL-C reductions approaching those achieved with injectable monoclonal antibodies while maintaining a favorable short-term safety profile. Early clinical studies have shown dose-dependent LDL-C reductions of approximately 50–60% when administered alongside statin therapy, suggesting that oral small molecules can achieve clinically meaningful lipid lowering without compromising efficacy. This expands therapeutic options for patients who require additional LDL-C reduction despite maximally tolerated statin therapy.

Another important advantage is the possibility of earlier treatment intensification. Since oral medications are generally easier to prescribe, dispense, and accept than injectable biologics, clinicians may be more inclined to introduce PCSK9 inhibition before prolonged treatment delays occur. Furthermore, oral agents eliminate injection-site reactions and reduce the logistical

burden associated with cold-chain storage and self-administration, potentially improving accessibility in routine clinical practice.

From a pharmaceutical perspective, orally administered macrocyclic peptides represent an innovative therapeutic platform that may broaden the future development of oral biologics. Successful oral delivery technologies developed for PCSK9 inhibitors could facilitate the development of additional orally active peptide-based therapies across various chronic diseases. (20)

Challenges:

Despite encouraging clinical results, oral PCSK9 inhibitors remain at an early stage of clinical development and several important limitations must be addressed before widespread clinical implementation. Most available evidence is derived from phase I and phase II clinical trials with relatively short follow-up durations. Consequently, long-term efficacy, durability of LDL-C reduction, and long-term safety remain uncertain.

Unlike injectable monoclonal antibodies, oral PCSK9 inhibitors currently lack dedicated cardiovascular outcome trials demonstrating reductions in major adverse cardiovascular events. Although substantial LDL-C lowering strongly suggests cardiovascular benefit, confirmation through adequately powered outcome studies remains essential before these agents can be fully integrated into clinical guidelines.

Drug formulation also presents unique challenges. Enlicitide is a macrocyclic peptide that requires specialized oral delivery technology to overcome degradation within the gastrointestinal tract and facilitate intestinal absorption. Oral peptide therapeutics generally exhibit poor bioavailability because of enzymatic degradation, acidic gastric conditions, limited epithelial permeability, and the intestinal mucus barrier. To overcome these physiological obstacles, advanced formulation strategies—including permeation enhancers, enteric coatings, enzyme inhibitors, peptide cyclization, and lipidation—are required, increasing manufacturing complexity. (20,21)

Additionally, oral dosing may require strict administration conditions, including fasting before dosing and delayed food intake, which could influence adherence in everyday clinical practice. Daily administration may also reduce convenience compared with long-acting injectable therapies such as inclisiran, which is administered only twice yearly.

Current Barriers:

Several barriers continue to limit the translation of oral PCSK9 inhibitors into routine clinical practice. Although enlicitide has received regulatory approval, other oral PCSK9 inhibitors remain under clinical investigation. Long-term real-world effectiveness, cost-effectiveness, and broader global accessibility remain important challenges

Economic considerations also remain important. Although oral formulations may eventually reduce administration-related costs, manufacturing macrocyclic peptides with specialized absorption technologies remains technically demanding. The pricing strategy of future oral PCSK9 inhibitors will therefore play a major role in determining their accessibility. Previous experience with injectable PCSK9 inhibitors demonstrated that high acquisition costs and restrictive reimbursement policies substantially limited patient access despite proven clinical efficacy.

Real-world evidence is another major gap. Current knowledge is derived almost entirely from controlled clinical trials, and evidence regarding

long-term adherence, treatment persistence, effectiveness across diverse patient populations, and healthcare utilization remains unavailable. Furthermore, clinicians will require guidance regarding optimal patient selection and positioning of oral PCSK9 inhibitors relative to statins, ezetimibe, bempedoic acid, inclisiran, and injectable monoclonal antibodies.(19,22)

Overall, while oral PCSK9 inhibitors have the potential to transform lipid management by combining potent LDL-C reduction with the convenience of oral administration, successful clinical adoption will depend on confirmation of long-term cardiovascular benefit, favorable cost-effectiveness, regulatory approval, and the generation of robust real-world evidence.

FUTURE PERSPECTIVES

The emergence of oral PCSK9 inhibitors marks an important advancement in lipid-lowering therapy, with the potential to overcome several limitations associated with injectable biologics. Although early clinical studies have demonstrated substantial reductions in LDL-C and favorable safety profiles, several aspects require further investigation before these agents can be fully integrated into routine clinical practice. Future research should focus on confirming long-term efficacy, cardiovascular benefits, optimizing patient selection, and developing next-generation oral agents with improved pharmacological characteristics.

Ongoing Phase III Trials:

Several oral PCSK9 inhibitors continue to progress through late-stage clinical development, reflecting the growing interest in expanding therapeutic options for hypercholesterolemia**.** Enlicitide (MK-0616), the first approved oral PCSK9 inhibitor, demonstrated consistent LDL-C reductions of approximately 55–60% in Phase II and Phase III clinical trials while maintaining an acceptable safety profile. The successful CORALreef Lipids and CORALreef-HeFH trials supported its regulatory approval and established its role as an effective oral lipid-lowering therapy. The ongoing CORALreef Outcomes trial is evaluating whether long-term treatment with enlicitide reduces major adverse cardiovascular events (MACE) in high-risk patients. The results of this study are expected to further define the long-term cardiovascular benefits of enlicitide and strengthen its role in the management of hypercholesterolemia. (1)

Beyond enlicitide, other oral agents continue to advance through clinical development. Laroprovstat (AZD0780) has entered Phase III evaluation after demonstrating dose-dependent LDL-C reductions and favorable tolerability in earlier studies. Additional compounds, including DC371739 and CVI-LM001, remain in earlier phases of development but have shown promising lipid-lowering efficacy and novel mechanisms of PCSK9 inhibition. Collectively, these trials will determine the long-term efficacy, safety, and optimal positioning of oral PCSK9 inhibitors in lipid management strategies. (23)

Cardiovascular Outcomes:

While LDL-C reduction is an established surrogate marker for cardiovascular risk reduction, demonstrating improvements in clinical outcomes remains essential for widespread adoption of oral PCSK9 inhibitors. Injectable PCSK9 inhibitors, including evolocumab and alirocumab, have already shown significant reductions in cardiovascular events, establishing PCSK9 inhibition as an effective therapeutic strategy. Whether oral agents can provide comparable cardiovascular protection remains to be confirmed through dedicated outcome trials.

The ongoing CORALreef Outcomes trial is specifically designed to determine whether enlicitide reduces the incidence of cardiovascular death, myocardial infarction, ischemic stroke, acute limb ischemia, major amputation, and urgent arterial revascularization in patients at high cardiovascular risk. Positive findings from this trial would establish oral PCSK9 inhibitors not only as potent lipid-lowering agents but also as therapies capable of improving long-term cardiovascular outcomes, thereby strengthening their role in contemporary preventive cardiology. (23)

Personalized Therapy:

Advances in precision medicine are expected to influence the future use of oral PCSK9 inhibitors. Individual variability in cardiovascular risk, genetic background, baseline LDL-C levels, statin tolerance, and treatment adherence may help identify patients who derive the greatest benefit from oral PCSK9 inhibition. Patients with familial hypercholesterolemia, established atherosclerotic cardiovascular disease, or persistent hypercholesterolemia despite maximally tolerated statin therapy may represent ideal candidates for these agents.

Future integration of pharmacogenomics, biomarkers, and cardiovascular risk prediction tools may further personalize lipid-lowering therapy by selecting the most appropriate patients and optimizing treatment intensity. Such individualized approaches have the potential to improve therapeutic outcomes while minimizing unnecessary treatment and healthcare costs.(16)

Combination Therapy:

Oral PCSK9 inhibitors are expected to become an important component of combination lipid-lowering strategies rather than replacing existing therapies. Because they act through mechanisms complementary to statins, ezetimibe, and bempedoic acid, combined treatment may achieve greater LDL-C reductions than monotherapy while helping more patients attain guideline-recommended lipid targets. Earlier studies have already demonstrated enhanced LDL receptor activity and additive lipid-lowering effects when oral PCSK9 inhibitors are used alongside statins. (24)

Future clinical trials should evaluate the long-term efficacy, safety, and cost-effectiveness of these combination regimens in diverse patient populations. Combination therapy may be particularly valuable for patients at very high cardiovascular risk, those with familial hypercholesterolemia, and individuals who fail to achieve target LDL-C concentrations despite conventional lipid-lowering treatment.

Future Drug Development:

The future of PCSK9-targeted therapy extends beyond currently available oral inhibitors. Ongoing research aims to develop newer oral molecules with improved oral bioavailability, greater potency, enhanced selectivity, fewer food-related absorption limitations, and simplified dosing regimens. Additionally, alternative therapeutic approaches, including gene-editing technologies, RNA-based therapies, and PCSK9-targeted vaccines, are being actively investigated as potential strategies for achieving long-term or even permanent suppression of PCSK9 activity. (25)

Although injectable monoclonal antibodies and siRNA therapies remain highly effective, future oral agents may offer improved patient convenience, broader accessibility, and potentially lower treatment costs. Continued innovation in drug design and results from ongoing clinical trials will determine the future position of oral PCSK9

inhibitors within lipid-lowering therapy. If long-term safety and cardiovascular benefits are confirmed, these agents have the potential to become a major component of dyslipidemia management and significantly expand treatment options for patients at increased cardiovascular risk.

CONCLUSION

Oral PCSK9 inhibitors represent a promising advancement in lipid-lowering therapy, offering the potential to combine potent LDL-C reduction with the convenience of oral administration. Among the currently available candidates, enlicitide has demonstrated robust and sustained reductions in LDL-C, non-HDL cholesterol, apolipoprotein B, and lipoprotein(a), while maintaining a favorable safety profile in clinical trials. Other emerging agents, including AZD0780, DC371739, and CVI-LM001, further highlight the expanding therapeutic landscape of oral PCSK9 inhibition.

Despite these encouraging findings, several challenges remain before these agents can be widely adopted in clinical practice. Long-term cardiovascular outcome data, real-world effectiveness, cost-effectiveness, and regulatory approval are still awaited. Ongoing Phase III and cardiovascular outcome trials will be critical in establishing their role alongside existing lipid-lowering therapies and determining their impact on reducing cardiovascular morbidity and mortality.

Overall, oral PCSK9 inhibitors have the potential to transform the management of hypercholesterolemia by improving treatment accessibility, patient acceptance, and adherence. Continued advances in drug development and the successful completion of ongoing clinical trials are expected to define their future position in personalized lipid management and cardiovascular disease prevention.

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