# Research Progress of PCSK9 Inhibitors in the Treatment of Coronary Heart Disease:Mechanisms of Action, Clinical Evidence, and Future Directions

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**Abstract**

Coronary heart disease (CHD) remains a chronic disease with high morbidity and mortality worldwide, with atherosclerosis serving as its fundamental pathological basis. Lowering low-density lipoprotein cholesterol (LDL-C) continues to be one of the most effective strategies for reducing atherosclerosis and preventing cardiovascular events. Although statins and ezetimibe are widely used in clinical practice, a considerable proportion of high-risk patients still fail to achieve optimal LDL-C control or are unable to tolerate conventional lipid-lowering therapy because of adverse effects. The development of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors has provided a novel and highly effective therapeutic strategy for the secondary prevention of CHD.This review systematically summarizes the physiological functions of PCSK9 and its pathological role in the development of CHD. It further integrates recent advances in PCSK9 inhibitor research, with particular emphasis on the mechanisms of action, pharmacokinetic characteristics, clinical outcomes, safety profiles, and clinical evidence of monoclonal antibodies and small interfering RNA (siRNA)-based agents. In addition, future research directions are discussed from the perspectives of treatment accessibility, long-term efficacy, combination therapy, and the development of novel therapeutic targets. Overall, PCSK9 inhibitors have emerged as a highly promising therapeutic option in the management of CHD. However, their clinical value should not be regarded merely as that of more potent lipid-lowering agents, but should also be explored in the contexts of personalized medicine, inflammation modulation, and long-term cardiovascular protection.

**Key words**

PCSK9; coronary heart disease; LDL-C; PCSK9 inhibitors; inclisiran; lipid-lowering therapy

# 1. Introduction

Coronary heart disease (CHD) is a group of disorders characterized by myocardial ischemia, hypoxia, and even necrosis resulting from coronary atherosclerosis. It remains one of the leading causes of morbidity and mortality among cardiovascular diseases worldwide. Extensive evidence from evidence-based medicine has demonstrated that elevated low-density lipoprotein cholesterol (LDL-C) is a major risk factor for the development and progression of CHD, and that sustained reduction of LDL-C significantly lowers the risk of atherosclerotic cardiovascular disease (ASCVD) events.

The management of CHD has long focused on controlling cardiovascular risk factors, among which LDL-C reduction is recognized as the most effective intervention for preventing cardiovascular events. Statins have served as the cornerstone of lipid-lowering therapy and have played an indispensable role in both the primary and secondary prevention of CHD. However, despite the use of high-intensity statin therapy, many patients fail to achieve the recommended LDL-C targets. In addition, some patients experience statin-associated muscle symptoms, limiting the effectiveness of conventional lipid-lowering strategies. Consequently, the identification of novel therapeutic targets and treatment approaches has become a major focus of cardiovascular research in recent years.

Against this background, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors have emerged as a major breakthrough in lipid-lowering therapy. Their potent and predictable LDL-C-lowering effects, together with their additional protective benefits against atherosclerotic cardiovascular events, have attracted considerable clinical attention.

As a key regulator of low-density lipoprotein receptor (LDLR) metabolism, PCSK9 has rapidly become a major focus of lipid metabolism research since its discovery. Monoclonal antibody-based PCSK9 inhibitors, in particular, have demonstrated remarkable efficacy in reducing LDL-C levels while maintaining favorable safety profiles, thereby providing a novel therapeutic option for patients with CHD.

To date, PCSK9 inhibitor therapy has evolved from early clinical investigations to an established treatment modality. Therapeutic approaches have expanded from monoclonal antibodies to small interfering RNA (siRNA)-based therapies and even vaccine strategies. This review comprehensively summarizes the current progress of PCSK9 inhibitors in the treatment of CHD from the perspectives of molecular pharmacology, clinical evidence, and future developments, with a particular focus on their mechanisms of action.

# 2. Biological Functions of PCSK9 and Its Role in Coronary Heart Disease

## 2.1 Structure and Function of PCSK9

Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a serine protease predominantly secreted by the liver. Its primary function is to bind to the low-density lipoprotein receptor (LDLR) and promote its degradation, thereby reducing the

liver's capacity to remove circulating low-density lipoprotein cholesterol (LDL-C).

Under normal physiological conditions, LDLRs are expressed on the surface of hepatocytes, where they bind circulating LDL-C and internalize it through receptor-mediated endocytosis. Following cellular uptake, LDL-C dissociates from LDLR within endosomes, allowing the receptor to recycle back to the cell surface for subsequent rounds of LDL-C clearance. However, when PCSK9 binds to LDLR, it alters the receptor's intracellular trafficking, directing it to lysosomal degradation rather than recycling. Consequently, the number of LDLRs on the hepatocyte surface decreases, resulting in reduced hepatic clearance of LDL-C and elevated plasma LDL-C levels. Increased PCSK9 expression or activity therefore leads to higher circulating LDL-C concentrations, whereas loss-of-function mutations in PCSK9 markedly reduce plasma cholesterol levels.

The biological role of PCSK9 extends beyond simply promoting LDLR degradation. Recent studies have shown that PCSK9 is also involved in the regulation of very-low-density lipoprotein (VLDL) and apolipoprotein B (ApoB) metabolism. Furthermore, accumulating evidence suggests that PCSK9 participates in immune and inflammatory responses associated with atherosclerosis, indicating that PCSK9 inhibition may exert biological effects beyond LDL-C lowering alone.

## 2.2 Pathological Role of PCSK9 in Atherosclerosis

In addition to regulating LDL-C metabolism, PCSK9 may accelerate the development and progression of atherosclerosis through several mechanisms:

1. Promotion of inflammatory responses: PCSK9 enhances lipid uptake by macrophages, facilitating foam cell formation and contributing to the inflammatory progression of atherosclerotic plaques.

2. Endothelial dysfunction: Elevated PCSK9 expression has been associated with impaired endothelial function, which may promote vascular injury and atherogenesis.

3. Regulation of vascular smooth muscle cells: Emerging evidence suggests that PCSK9 may influence the proliferation and migration of vascular smooth muscle cells, thereby contributing to arterial remodeling.

These findings provide a more comprehensive explanation for the reduction in cardiovascular events observed with PCSK9 inhibitor therapy, suggesting that their clinical benefits extend beyond LDL-C reduction alone.

## 2.3 Genetic Evidence Supporting PCSK9 as a Therapeutic Target

Genetic studies have provided compelling evidence for the pivotal role of PCSK9 in lipid metabolism. Gain-of-function mutations in the PCSK9 gene cause familial hypercholesterolemia by increasing circulating LDL-C levels, whereas loss-of-function mutations are strongly associated with substantially lower LDL-C concentrations and a reduced risk of cardiovascular events.

Individuals who naturally carry PCSK9 loss-of-function variants exhibit lifelong reductions in LDL-C levels and a significantly lower incidence of coronary heart disease without apparent major safety concerns. This "natural experiment" has strengthened confidence in the long-term safety

of PCSK9 inhibition. Moreover, these genetic findings have not only validated PCSK9 as a rational therapeutic target but have also provided a solid scientific foundation for the development of PCSK9-targeted therapies.

# 3. Types of PCSK9 Inhibitors and Their Mechanisms of Action

## 3.1 Monoclonal Antibodies (mAbs)

The two most widely used monoclonal antibody (mAb) therapies are evolocumab and alirocumab. These agents exert their lipid-lowering effects by directly binding circulating PCSK9 in the plasma, thereby preventing its interaction with low-density lipoprotein receptors (LDLRs). As a result, LDLRs are recycled back to the hepatocyte surface instead of being degraded, allowing continued clearance of circulating LDL-C. Monoclonal antibodies typically produce an additional 50–60% reduction in LDL-C beyond standard lipid-lowering therapy.

These agents offer several important advantages, including rapid onset of action, substantial and predictable reductions in LDL-C levels, and broad clinical applicability, particularly for high-risk patients requiring secondary prevention of cardiovascular disease.

However, monoclonal antibody therapy also has several limitations. These agents must be administered by subcutaneous injection, resulting in relatively high treatment costs. In addition, patient adherence may vary considerably because of the need for repeated injections.

## 3.2 Small Interfering RNA (siRNA)

The most widely used small interfering RNA (siRNA) therapy is inclisiran, which utilizes RNA interference technology to inhibit the translation of PCSK9 messenger RNA (mRNA) in hepatocytes, thereby reducing PCSK9 synthesis at its source. By suppressing PCSK9 production upstream, inclisiran effectively lowers circulating LDL-C levels.

A major advantage of inclisiran is its exceptionally infrequent dosing schedule. After the initial and three-month doses, maintenance treatment requires administration only twice yearly, providing sustained LDL-C reduction with long-lasting therapeutic effects. This dosing regimen makes inclisiran particularly suitable for long-term lipid management and for patients with poor adherence to more frequent treatment schedules. Although its LDL-C-lowering efficacy is slightly less pronounced than that of monoclonal antibodies, its prolonged duration of action and improved treatment adherence offer substantial clinical advantages.

## 3.3 Emerging Therapies: PCSK9 Vaccines and Small-Molecule Inhibitors

In addition to established therapies, novel approaches targeting PCSK9 are currently under development, including PCSK9 vaccines and small-molecule inhibitors.

In theory, PCSK9 vaccines could induce long-lasting endogenous production of anti-PCSK9 antibodies, thereby providing a more cost-effective lipid-lowering strategy for large

populations. However, their long-term immunogenicity, safety, durability of protection, and controllability have yet to be fully established.

Small-molecule inhibitors represent another promising therapeutic strategy. Nevertheless, because it is technically challenging to achieve stable inhibition of the protein–protein interaction between PCSK9 and LDLR using small molecules, these agents remain in the early stages of preclinical and clinical development.

# 4. Clinical Evidence for PCSK9 Inhibitors in Coronary Heart Disease

## 4.1 LDL-C–Lowering Efficacy

Both monoclonal antibodies (mAbs) and small interfering RNA (siRNA)-based therapies have demonstrated substantial LDL-C reductions across multiple clinical studies. Most evidence indicates that mAbs provide an additional 50–60% reduction in LDL-C when added to statin therapy, whereas inclisiran achieves reductions of approximately 45–52%.

In addition to lowering LDL-C, both therapeutic approaches improve other atherogenic lipid parameters, including apolipoprotein B (ApoB), non-high-density lipoprotein cholesterol (non-HDL-C), and lipoprotein(a) [Lp(a)], further enhancing their clinical value in high-risk patients. Notably, the lipid-lowering effects of PCSK9 inhibitors are both durable and consistent. Even among patients with relatively low baseline LDL-C levels, further reductions can still be achieved. This characteristic makes PCSK9 inhibitors particularly valuable for patients with very high-risk CHD, especially those who experience recurrent cardiovascular events or have multiple cardiovascular risk factors.

Imaging studies have further suggested that the benefits of PCSK9 inhibitors extend beyond lipid lowering. Several intravascular ultrasound (IVUS) and coronary computed tomography (CT) studies have demonstrated that these agents may slow the progression of, or even induce regression of, coronary atherosclerotic plaque burden. These findings indicate that the clinical benefits of PCSK9 inhibitors may not be limited to numerical reductions in lipid levels but may also involve improvements in vascular structure and function.

In patients with acute coronary syndrome (ACS), several studies have investigated the feasibility of early initiation of PCSK9 inhibitor therapy. The available evidence suggests that early intensive lipid-lowering treatment may facilitate rapid plaque stabilization, attenuate vascular inflammation, and reduce the risk of short- and intermediate-term cardiovascular events. Although this strategy has not yet been fully incorporated into routine clinical guideline recommendations, it represents an important direction for future research.

## 4.2 Effects on Major Cardiovascular Events

A large body of clinical evidence has demonstrated that PCSK9 inhibitors significantly reduce the incidence of major adverse cardiovascular events (MACE), including myocardial infarction, stroke, coronary revascularization, and, in some studies, cardiovascular death, although reductions in cardiovascular mortality have not consistently reached statistical significance.

Overall, PCSK9 inhibitor therapy is associated with an approximate 10–20% reduction in

MACE, with even greater benefits observed in patients at very high cardiovascular risk.

Importantly, reductions in cardiovascular events often become evident relatively early after treatment initiation. This differs from the traditional concept that the cardiovascular benefits of lipid lowering accumulate only over prolonged periods, suggesting that mechanisms beyond LDL-C reduction—such as anti-inflammatory effects and plaque stabilization—may also contribute to the observed clinical benefits.

## 4.3 Efficacy in Special Populations

1. Familial hypercholesterolemia (FH): Patients with FH experience particularly pronounced reductions in LDL-C, and current clinical guidelines strongly recommend the use of PCSK9 inhibitors in appropriate high-risk individuals.

2. Patients with acute coronary syndrome (ACS): The reduction in cardiovascular events appears to be especially significant in patients treated after ACS, supporting the role of intensive lipid-lowering therapy during this high-risk period.

3. Statin-intolerant patients: For patients who are unable to tolerate statins because of adverse effects, PCSK9 inhibitors represent one of the most effective and well-tolerated alternative lipid-lowering therapies.

# 5. Safety and Tolerability

Overall, PCSK9 inhibitors have demonstrated an excellent safety profile, although several adverse events have been reported, including injection-site reactions, nasopharyngitis, and mild elevations in liver enzyme levels.

To date, no clear evidence has linked PCSK9 inhibitors to clinically significant myotoxicity or neurocognitive impairment. Moreover, long-term genetic evidence supports the safety of sustained PCSK9 inhibition.

Concerns regarding potential adverse effects on neurocognitive function, glucose metabolism, and immune responses have not been substantiated by long-term follow-up studies. These findings have largely alleviated concerns that achieving extremely low LDL-C levels might result in clinically significant safety risks.

From a clinical perspective, the favorable tolerability of PCSK9 inhibitors makes them an important therapeutic alternative for patients with statin intolerance and supports their use in long-term intensive lipid-lowering therapy.

Nevertheless, whether profound LDL-C reduction may influence steroid hormone synthesis or nervous system function remains uncertain. Although no definitive safety signals have been identified to date, continued long-term surveillance is warranted. Overall, current evidence indicates that PCSK9 inhibitors are well tolerated, with adverse event rates comparable to those observed in placebo groups. Injection-site reactions remain the most common adverse event; these are generally mild to moderate in severity and rarely lead to treatment discontinuation.

# 6. Observations from Real-World Clinical Practice

In routine clinical practice, the use of PCSK9 inhibitors exhibits several characteristics that differ from those observed in randomized clinical trials.

1. Treatment adherence is closely associated with dosing frequency. Because inclisiran

requires only twice-yearly maintenance administration, patient adherence is generally higher than that observed with monoclonal antibody therapies requiring more frequent injections.

2. Cost and accessibility remain the major barriers to widespread use. In many regions, the high cost of PCSK9 inhibitors limits their availability, particularly in primary healthcare institutions and community-based medical settings.

3. A gap exists between guideline recommendations and real-world implementation. Many patients who meet the criteria for PCSK9 inhibitor therapy are either not appropriately identified or do not receive treatment.

Therefore, future treatment strategies should strive to achieve an optimal balance among therapeutic efficacy, patient adherence, and cost-effectiveness.

# 7. Future Directions and Perspectives

## 7.1 From Potent Lipid Lowering to Multi-Target Cardiovascular Protection

Current research is investigating whether PCSK9 inhibition provides benefits beyond LDL-C reduction, including attenuation of inflammation, enhancement of plaque stability, and promotion of endothelial repair. Confirmation of these additional cardioprotective mechanisms would substantially broaden the clinical applications of PCSK9 inhibitors, extending their therapeutic value beyond coronary heart disease to other cardiovascular conditions involving related pathological pathways.

## 7.2 Optimization of Personalized Treatment Strategies

Personalized medicine is expected to play an increasingly important role in the application of PCSK9-targeted therapies. Genetic testing may help identify patients most likely to benefit from PCSK9 inhibition, while circulating PCSK9 levels may serve as potential biomarkers for treatment selection. Future therapeutic strategies may therefore evolve from treatment decisions based solely on LDL-C levels to approaches guided by individual molecular targets and genetic characteristics.

## 7.3 Reducing Treatment Costs and Expanding Accessibility

The development of PCSK9 vaccines, small-molecule inhibitors, and more economical drug delivery strategies represents an important direction for future research. If treatment costs can be substantially reduced, PCSK9 inhibitors may expand beyond their current use in patients at very high cardiovascular risk and become more widely available for broader preventive applications across diverse healthcare settings.

## 7.4 Combination Therapy Strategies

Future therapeutic approaches are likely to involve combination regimens, such as:

PCSK9 inhibitors plus anti-inflammatory agents

PCSK9 inhibitors plus lipoprotein(a) [Lp(a)]-targeted therapies

PCSK9 inhibitors plus glucagon-like peptide-1 receptor agonists (GLP-1R agonists) for patients with obesity or metabolic syndrome

Such combination strategies have the potential to achieve truly multitarget interventions for the prevention and treatment of atherosclerotic cardiovascular disease, thereby further improving long-term cardiovascular outcomes.

# 8. Conclusion

In summary, PCSK9 inhibitors achieve potent and sustained reductions in low-density lipoprotein cholesterol (LDL-C) through a well-defined and unique mechanism of action, while significantly reducing the risk of cardiovascular events in patients with coronary heart disease (CHD). Extensive clinical evidence has confirmed their efficacy and favorable safety profile, establishing PCSK9 inhibitors as an important addition to contemporary lipid-lowering therapy.

However, the future role of PCSK9 inhibitors should extend beyond simply providing more intensive LDL-C reduction. Greater emphasis should be placed on integrating these agents into personalized treatment strategies, exploring mechanisms beyond lipid lowering, developing combination therapies targeting complementary pathways, and improving their affordability and accessibility in routine clinical practice.

Only through these advances can PCSK9 inhibitors realize their full potential and become a cornerstone of comprehensive coronary heart disease management.

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