Advances in the Clinical Application of Novel PCSK9 Inhibitors for High-Risk Atherosclerotic Cardiovascular Disease

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Abstract. Dyslipidemia is a major contributor to atherosclerotic cardiovascular disease (ASCVD), the leading cause of morbidity and mortality worldwide. Proprotein convertase subtilisin/kexin type 9 (PCSK9) promotes hepatic low-density lipoprotein receptor (LDLR) degradation, elevating plasma low-density lipoprotein cholesterol (LDL-C) and contributing to plaque initiation, progression, and destabilization via lipid-dependent and -independent pathways (e.g., inflammation, endothelial dysfunction, thrombosis). PCSK9 inhibition is a validated target for intensive lipid management Beyond statins, monoclonal antibodies (evolocumab, alirocumab) and siRNA-based therapy (inclisiran) achieve reductions in LDL-C of >50%. Large outcome trials (FOURIER, ODYSSEY OUTCOMES, ORION series) have demonstrated reduced major adverse cardiovascular events (MACE) and favorable safety in high-risk populations including acute coronary syndrome, familial hypercholesterolemia, and statin intolerance. Newer approaches include oral small molecule inhibitors (e.g., MK-0616, AZD0780), therapeutic vaccines (e.g., AT04A), and gene-editing (e.g., VERVE-101) with improved adherence, durability or potential cure. For patients with very-high-risk or high-risk ASCVD who do not achieve LDL-C targets with traditional therapies, clinical guidelines, including China-specific recommendations, support the use of PCSK9 inhibitors to lower LDL-C and further reduce CV risk.

Keywords: Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors; Low-density lipoprotein cholesterol (LDL-C); Atherosclerosis; Lipid-lowering therapy; Cardiovascular risk reduction.

1. ASCVD Burden, Unmet Needs, and the Role of PCSK9

Atherosclerotic cardiovascular disease (ASCVD) represents a major chronic inflammatory condition and constitutes a substantial global health burden. In China, CVD remains the leading cause of death, accounting for approximately 45–48% of all deaths in recent years, with an estimated >4–5 million CVD deaths annually and a persistently high burden from ASCVD subtypes such as ischemic heart disease and stroke, particularly amid population aging and metabolic risks [1]. Elevated LDL-C is a central modifiable risk factor, yet among high-risk and very-high-risk ASCVD populations, a substantial proportion of patients still fail to achieve guideline-recommended LDL-C targets or experience intolerance/suboptimal response to statin-ezetimibe therapy, maintaining elevated residual cardiovascular risk [2].

Elevated LDL-C is an important modifiable risk factor; however, relatively few patients with high- and very-high-risk atherosclerotic cardiovascular disease (ASCVD) achieve guideline-recommended LDL-C targets or are intolerant to (or have suboptimal response to) statin-ezetimibe therapy and therefore remain at elevated residual cardiovascular risk.[3, 4]. Gain-of-function mutations in PCSK9 are causal for autosomal dominant hypercholesterolemia [5], and the E670G polymorphism has been associated with increased coronary heart disease risk in the Chinese Han population; in contrast, loss-of-function variants confer lifelong reductions in LDL-C and are associated with markedly attenuated ASCVD risk [6]. Besides LDL-C elevation, PCSK9 has direct pro-atherogenic effects by promoting vascular inflammation, platelet activation, and thrombosis, which further contribute to atherosclerotic progression and events. These results have unequivocally confirmed PCSK9 as a major therapeutic target and pharmacologic inhibition of PCSK9 as one of the best validated mechanisms to accomplish LDL-C lowering beyond traditional statin therapy.

In the last decades, the introduction of lipid-lowering therapies such as statins and ezetimibe has determined a dramatic increase of LDL-C target achievement rate and a significant reduction of the

incidence of acute coronary events. The clinical approval of monoclonal antibodies targeting PCSK9 (evolocumab, alirocumab) and small interfering RNA-based therapeutics (inclisiran) has established PCSK9-inhibition as a cornerstone of evidence-based lipid management after statin therapy. In major cardiovascular outcome trials, including FOURIER, ODYSSEY OUTCOMES, and the ORION series (9/10/11), additional reductions in LDL-C of 50%-60% and significant lowering of major adverse cardiovascular events (MACE) have been consistently demonstrated with a favorable safety profile in high-risk populations, including those with diabetes, chronic kidney disease, and familial hypercholesterolemia, as well as early intervention after ACS [6, 7].

The past few years have seen major advances in understanding the molecular mechanisms, clinical efficacy, safety profile and population-specific utility of PCSK9 inhibitors. This article provides a systematic review of data on the mechanistic basis and key findings of major clinical trials of PCSK9 inhibitors in high-risk ASCVD populations with particular emphasis on current applications in patients with acute coronary syndrome (ACS), familial hypercholesterolemia (FH), and statin intolerance. We additionally review emerging paradigms for personalized therapeutic selection, describe emerging therapeutic modalities in development, and identify directions for future research. The general aim is to provide evidence-based, accurate and clinically relevant information to guide the optimization of lipid-lowering therapy in practice.

2. Molecular Mechanisms and Signaling Pathways of PCSK9

PCSK9 inhibition is an established therapeutic strategy for LDL-C reduction in ASCVD populations. The molecular and signaling pathways involved in the pathophysiological effects of PCSK9 are as follows (see Figure 1). They are explained in the following sections to provide a mechanistic rationale for its pharmacological targeting.

2.1. The Canonical Lipid-Metabolic Axis: The PCSK9–LDLR Pathway

The hepatic LDLR contains an EGF-A domain that binds circulating PCSK9 with high affinity. PCSK9 is a protein that is primarily produced and secreted by hepatocytes. This interaction leads to internalization and lysosomal degradation of the receptor–ligand complex, reducing LDLR recycling and increasing plasma LDL-C levels [8, 9]. Besides systemic endocrine effect, PCSK9 locally produced by vascular smooth muscle cells (VSMCs) can downregulate LDLR expression in macrophages via paracrine signaling. This process impairs cellular cholesterol uptake and may contribute to foam cell formation, indicating the presence of an autoregulatory lipid-modulatory network within the vascular wall [8].

2.2. The Non-lipid Inflammatory Axis: TLR4/NF-κB Signaling Network

Besides its canonical role in lipid metabolism, PCSK9 has lipid-independent effects, particularly in promoting vascular inflammation. PCSK9 directly interacts with Toll-like receptor 4 (TLR4) and triggers phosphorylation and degradation of IκBα. This leads to nuclear translocation of NF-κB, and induction of expression of pro-inflammatory genes such as TNF-α, IL-1β and MCP-1 [10, 11]. In apoE$^{-/-}$ mouse models, preclinical data show that genetic suppression of PCSK9 significantly reduces aortic plaque area and macrophage infiltration, without significantly altering lipid profiles, suggesting that its pro-inflammatory effects are independent of cholesterol metabolism. Hemodynamic shear stress further modulates the regulatory axis. Low shear stress (3–6 dynes/cm 2) enhances PCSK9 expression via NADPH oxidase-dependent reactive oxygen species (ROS). forming a positive feedback loop of “low shear–ROS–PCSK9–inflammation”. This constitutes a positive feedback loop of "low shear-ROS-PCSK9-inflammation", providing a novel theoretical basis for the preferential development of atherosclerosis at vascular bifurcation sites [9].

2.3. The Thrombotic and Coagulation Regulatory Axis: Dual Targeting of CD36 and LRP1

PCSK9 also promotes thrombotic complications, independently of lipid levels, by modulating platelet function and coagulation . PCSK9 in circulation binds directly to CD36 on platelets, activating a signaling cascade, which, in turn, activates Src kinase, MAPK pathways (ERK5/JNK), and p38/cPLA2/COX-1/TXA_2, which promotes platelet aggregation, granule secretion, and thrombus formation in vivo. This prothrombotic effect is entirely abolished in CD36−/− mouse models and with aspirin pharmacological inhibition demonstrating it is CD36-mediated signaling-dependent [12].

At the same time, PCSK9 inhibitors have anticoagulant effects via a different, lipid-independent mechanism. These agents increase hepatic LRP1 expression and promote clearance of coagulation factor VIII (FVIII) by attenuating PCSK9-mediated degradation of LDL receptor-related protein 1 (LRP1) with a consequent reduction in plasma FVIII levels and a corresponding reduction in the risk of venous thromboembolism [13]. This modulation of the two pathways, one that targets platelet hyperreactivity and the other the homeostasis of coagulation factors, provides a mechanistic rationale for the reduction of thrombotic events observed in clinical trials and supports the notion of precision antithrombotic strategies [13].

These non-lipid effects (inflammation, thrombosis) may explain the early and sustained reductions in major adverse cardiovascular events (MACE) seen in large outcome trials (e.g., FOURIER, ODYSSEY OUTCOMES) beyond what would be predicted by LDL-C lowering alone, as benefits often occur rapidly and persist across subgroups despite modest differences in achieved LDL-C .

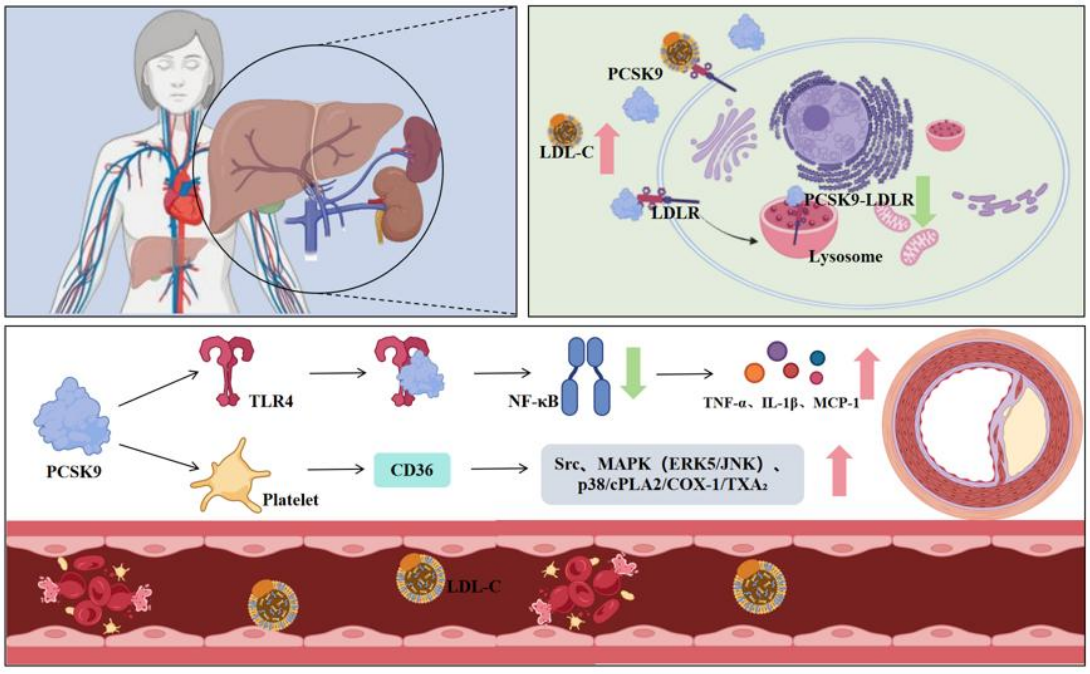

Figure 1: Schematic Overview of PCSK9's Molecular Mechanisms in ASCVD Pathophysiology. Illustration of PCSK9's canonical (LDLR degradation), inflammatory (TLR4/NF-κB), and thrombotic (CD36 signaling) pathways, contributing to elevated LDL-C, vascular inflammation, platelet activation, and atherosclerosis.

3. Progress in Clinical and Preclinical Investigations of Diverse PCSK9 Inhibitor Modalities

PCSK9 has emerged as a major therapeutic target for LDL-C lowering, and has led to rapid drug development. A number of different technological platforms including monoclonal antibodies, small interfering RNA (siRNA) therapeutics, orally bioavailable small molecules, peptide-based vaccines and genome editing technologies, all hold promise for improving outcomes in ASCVD. This section looks at their developmental trajectories.

3.1. Monoclonal Antibodies

3.1.1. Alirocumab

Alirocumab, a representative PCSK9 inhibitor, showed a strong clinical efficacy and a good safety profile in the secondary prevention of major adverse cardiovascular events in various high-risk populations. In the ODYSSEY OUTCOMES Phase III trial (n≈18,600), there was incremental cardiovascular risk reduction in patients with recent ACS on high-intensity statin therapy [14]. Longitudinal data suggest that sustained attainment of very low LDL-C levels is associated with improved clinical outcomes [14]. Post-hoc analyses suggest that the absolute cardiovascular benefit is greater in patients with high baseline triglyceride (TG) levels, but TG reduction does not contribute to risk modification in isolation, highlighting LDL-C lowering as the primary mechanistic pathway for alirocumab's cardioprotective effects [15].

Alirocumab has therapeutic utility in other high risk cohorts. When combined with standard medical therapy, alirocumab significantly reduces major atherogenic lipid parameters, including LDL-C and lipoprotein (a) [Lp(a)] in patients with ACS with concomitant HF and non-ST-elevation myocardial infarction (NSTEMI) and in adults with homozygous familial hypercholesterolaemia (HoFH) [16-18].

3.1.2. Evolocumab

Evolocumab causes substantial reductions in circulating LDL-C concentrations by specific inhibition of PCSK9, which is the basis for its therapeutic effect [19]. In patients with established ASCVD and LDL-C levels ≥70 mg/dL (1.8 mmol/L) on maximally tolerated statin therapy, in the FOURIER Phase III trial (n≈27,500), evolocumab reduced LDL-C by 59% compared with placebo. Furthermore, treatment was associated with a significant decrease in the incidence of the primary composite endpoint and key secondary cardiovascular outcomes [20, 21].

The addition of a PCSK9 inhibitor, such as evolocumab, represents an evidence-based strategy for patients with persistent LDL-C elevation despite optimized statin regimens[20, 22]. This incremental lipid-lowering translates into reduced cardiovascular morbidity and mortality in the ASCVD population, with the magnitude of clinical benefit exhibiting a direct dose-response relationship to the absolute achieved reduction in LDL-C [23]. In alignment with contemporary clinical guidelines, early in-hospital initiation of high-intensity statin therapy following an acute cardiovascular event is recommended to mitigate the risk of early recurrent ischemic events [19, 24].

3.2. siRNA-Based Therapeutics: Inclisiran

siRNA, a therapeutic modality that harnesses the RNA interference pathway to mediate gene silencing, shows significant potential in the development of lipid-lowering therapeutics. Inclisiran, a siRNA agent, targets PCSK9 and effectively lowers plasma LDL-C levels by selectively silencing PCSK9 mRNA.

Inclisiran is a new therapeutic approach that uses a siRNA to target hepatic PCSK9 messenger RNA for degradation. Early phase studies demonstrated its ability to induce sustained reductions in LDL-C in healthy volunteers [25]. The subsequent ORION-1 trial confirmed the evidence that inclisiran is effective in reducing circulating PCSK9 and LDL-C concentrations in patients at high cardiovascular risk with inadequately controlled hypercholesterolemia, with therapeutic effects maintained during 180 days of follow-up [26].

The strong efficacy of inclisiran in lowering LDL-C has been consistently shown in Phase I and II clinical studies. Pharmacodynamic data show that a twice-yearly subcutaneous dosing schedule results in an average LDL-C reduction of about 50% versus approximately 30% with an annual dosing schedule [27]. The long-term efficacy, safety and tolerability profile of inclisiran (284 mg dose) was further supported in three Phase III ORION trials, which demonstrated persistent LDL-C lowering and sustained reduction of plasma PCSK9 levels of approximately 80% in high-risk cardiovascular populations [28, 29].

In the ORION-3 study, a 4-year open-label extension of the ORION-1 trial, long-term treatment with inclisiran led to a mean LDL-C reduction of 44.2% and a PCSK9 reduction of 62.2% to 77.8% during the observation period. In particular, in the treatment-switch cohort (patients switching from biweekly subcutaneous evolocumab 140 mg to inclisiran after the initial 360-day period), both therapeutic strategies showed similar efficacy and safety, without significant clinical differences between groups [30].

Clinical trials are increasingly showing that inclisiran may have benefits beyond lipid modulation. In a cohort of high-risk patients with persistently elevated LDL-C levels despite maximally tolerated statin therapy, patients randomized to inclisiran had a lower incidence of cardiovascular events compared with placebo. This suggests a possible role for inclisiran in reducing cardiovascular event rates, a hypothesis currently being tested in a rigorous manner in the dedicated cardiovascular outcomes trial ORION-4 [31].

3.3. Orally Administered Small Molecule Agents

Effective in lowering LDL-C levels are monoclonal antibodies and siRNA-based therapeutics termed PCSK9 inhibitors. However, long-term patient compliance is limited due to their parenteral administration. This has led to considerable scientific and clinical interest in the development of orally bioavailable PCSK9 inhibitors to provide more convenient and sustainable lipid-lowering regimens. As of 2026, some candidates are in late-stage development but none have been approved for clinical use by regulators.

MK-0616 is a macrocyclic peptide inhibitor of PCSK9 developed by mRNA display technology to interfere with the PCSK9-LDLR protein-protein interaction. Preclinical characterization showed a potent inhibitory constant (Ki = 5 pM) against human PCSK9. In a Phase 1 clinical study, a single oral dose of MK-0616 resulted in >93% reduction in circulating free PCSK9 concentrations in healthy subjects. In concomitant statin therapy subjects, once daily dosing for 14 days resulted in a mean LDL-C reduction of 60.5%, with efficacy similar to that observed with injectable PCSK9 inhibitor modalities [32]. Subsequent Phase IIb and several Phase III trials e.g., CORALreef Lipids, n large; 2025 data confirmed dose-dependent reductions of up to ~55-60% LDL-C at week 24 vs placebo, with a safety profile comparable to placebo, positioning it as a potential first-in-class oral PCSK9 inhibitor [33, 34].

AZD0780 is a different, oral small molecule scaffold of the C-terminal domain of PCSK9 that inhibits lysosomal sorting and degradation of LDLR. In the Phase II PURSUIT study, adjunctive once daily AZD0780 (1-30 mg) for 12 weeks resulted in dose-dependent reductions in LDL-C in patients on background statin therapy. The 30 mg dose group had a 50.7% reduction in LDL-C compared with placebo. The compound had a favorable safety and tolerability profile, with adverse event rates similar to placebo and no signal of hepatotoxicity or clinically significant dysglycemia [35]. Phase III evaluation (e.g. AZURE-LDL) is ongoing [35] as of 2025.

3.4. Vaccines

Vaccines directed against PCSK9 constitute a new therapeutic paradigm in the field of active immunoterapy aimed at overcoming the intrinsic limitations of monoclonal antibody–based strategies, such as the need for frequent parenteral administration and a considerable economic burden. That said, the progress is still in the preclinical and early clinical stage. This strategy is based on the provision of engineered PCSK9-derived immunogens that elicit a sustained, high-titer polyclonal antibody response. The resulting antibodies competitively inhibit PCSK9 binding to the LDLR, which promotes hepatic LDLR recycling and results in a sustained reduction in circulating LDL-C concentrations [36]. This therapeutic concept has been strongly validated by preclinical studies. A vaccine candidate (AT04A) developed by AFFIRIS AG based on its proprietary AFFITOPE platform showed pronounced efficacy in translational models [37]. Similarly, in APOE*3Leiden.CETP transgenic mice, a model that recapitulates key features of human lipoprotein metabolism and atherosclerosis, vaccination with AT04A led to a 53% reduction in total plasma cholesterol exposure

($P < 0.001$), a 64% reduction in atherosclerotic lesion area in the aortic root ($P = 0.004$), and a marked decrease in systemic inflammatory biomarkers (serum amyloid A, MIP-1β) and vascular inflammation [37]. Similar results were also reported in preclinical studies of other immunogen designs including peptide-based formulations and nanoparticle delivery systems (e.g. liposomal L-IFPTA+ construct) [38, 39].

This promising basis has made possible the transition to clinical evaluation. AFFIRIS AG has performed a first-in-human, single-blind, randomized, placebo-controlled Phase I study to evaluate the safety, immunogenicity and pharmacodynamic activity of two AFFITOPE® peptide vaccines, AT04A and AT06A. Both candidates showed a good tolerability profile, with injection site reactions (mostly mild to moderate) as the most frequent adverse events. Importantly, no activation of PCSK9-specific cytotoxic T-cells was observed, indicating a predominantly humoral and presumed safe immunological response. At the 15 μg dose, both vaccines elicited potent and sustained IgG antibody titers that were cross-reactive to the native PCSK9 epitope. A booster dose of 75 μg at week 60 after a 3-dose priming regimen (weeks 0, 4 and 8) successfully reactivated the antibody response, confirming the establishment of immunological memory. However, only AT04A showed a clinically meaningful lipid-lowering effect with a mean placebo-adjusted LDL-C reduction of 7.2% ($P < 0.0001$). This landmark study provides preliminary clinical proof-of-concept for active PCSK9 immunization and establishes AT04A as a lead candidate for further development [40].

Most of the work in this area is still in the preclinical and early clinical investigation stages, but overall the data highlight the great translational promise of PCSK9 vaccines. Their potential to provide effective, long-term lipid management with infrequent immunization (e.g., annual boosters) and potentially better cost-effectiveness and a favorable safety profile, makes this modality a promising future adjunctive or alternative strategy for the primary and secondary prevention of atherosclerotic cardiovascular disease [36].

3.5. Genome Editing Therapeutics

The rapid development of genome editing technologies has converted in vivo PCSK9-targeted genetic intervention into a revolutionary paradigm for the management of dyslipidemia. Early proof-of-concept used CRISPR/Cas9 to inactivate Pcsk9 in murine models yielding 35–40% cholesterol reduction [41]. This therapeutic principle has been advanced by next generation precision genetic tools, with the focus shifting to VERVE-102 (an in vivo adenine base editor; VERVE-101 largely deprioritized following earlier safety signals including transient liver enzyme elevations and thrombocytopenia) [42]. VERVE-102 seeks to achieve permanent transcriptional silencing of the PCSK9 gene in hepatocytes by employing precise base conversion, which may result in lifelong LDL-C attenuation without DNA double-strand breaks [43].

Preclinical assessment in non-human primates showed sustained reductions in LDL-C up to 69% with no detectable off-target germline editing and a promising long-term safety and tolerability profile [44].

It is in translation to clinical assessment. Interim data from the Phase 1b Heart-2 trial (2025) in patients with HeFH/premature CAD demonstrated dose-dependent reductions: mean LDL-C reduction of 53% (maximum 69%) at the 0.6 mg/kg dose, with PCSK9 reduction of ~60%, and no treatment-related serious adverse events or clinically significant laboratory abnormalities [43]. Trial is ongoing at a dose escalation (0.7 mg/kg cohort) with final data expected in late 2025 and Phase II initiation planned thereafter.

If proven effective and safe in further clinical development, and if potential ethical issues such as off-target editing risks (none observed to date) are addressed, PCSK9 genome editing could eventually provide a paradigm-shifting, single-course therapeutic alternative in high-risk populations. This approach has the potential to fundamentally bypass the limitations of chronic pharmacotherapy, namely poor long-term adherence and the cumulative burden of lifelong treatment.

4. Clinical Application Guidelines for PCSK9 Inhibitors

Standardized use of PCSK9 inhibitors in patients with ASCVD is an important step to guarantee therapeutic efficacy and safety. The following sections will systematically elaborate on their indications, timing of initiation, and long-term management strategies, based on current major clinical guidelines and consensus statements.

Expert Consensus on the Clinical Medication Management Pathway for Patients with Coronary Atherosclerotic Heart Disease (2023) states that all patients with coronary heart disease should receive interventions for dietary control and lifestyle improvement, and on this basis, undergo lipid-regulating therapy primarily based on statins. Considering that the tolerance of the Chinese population to statins is lower than that of Western populations, it is recommended to develop individualized pharmacotherapy plans according to the specific circumstances of the patient. Before initiating drug therapy, baseline levels of blood lipids, transaminases, and creatine kinase should be measured, and the required magnitude of LDL-C reduction should be estimated based on the baseline and target LDL-C values.

Required reduction < 50%: Initiate a moderate-intensity statin and re-evaluate after 4–6 weeks; if the target is met, maintain, if not, increase to the maximum tolerated dose of statin; if the target is still not met, and if achieving the target is anticipated with the addition of ezetimibe, it is recommended to combine the statin with ezetimibe; otherwise, directly initiate combination therapy with the statin and a PCSK9 inhibitor; if LDL-C remains non-compliant after 4–6 weeks of statin combined with ezetimibe therapy, it is recommended to add a PCSK9 inhibitor.

Required reduction ≥ 50%: It is recommended to initiate treatment with the maximum tolerated dose of a statin combined with ezetimibe, and re-evaluate after 4–6 weeks to assess lipid goal attainment and tolerance; if the target is met, it can be continued, if not, gradually increase to the maximum tolerated dose of statin based on individual circumstances, and re-evaluate goal attainment 4–6 weeks after dose adjustment; for patients whose LDL-C levels remain non-compliant after 4–6 weeks of statin combined with ezetimibe therapy, it is recommended to add a PCSK9 inhibitor [45].

The Chinese Guidelines for Lipid Management (2023) recommend using LDL-C as the primary target for ASCVD risk intervention. The guidelines also state that when statins or Xuezhikang(a red yeast rice-derived statin-like agent commonly used in China) fail to achieve LDL-C goals, non-statin lipid-lowering drugs, such as cholesterol absorption inhibitors or PCSK9 inhibitors, can be used in combination. For ultra-high-risk patients, when baseline LDL-C is elevated (LDL-C ≥ 4.9 mmol/L in patients not on statin therapy; or LDL-C ≥ 2.6 mmol/L in patients on statin therapy), and it is anticipated that combination therapy with a statin and a cholesterol absorption inhibitor will not achieve the LDL-C target, direct initiation of combination therapy with a statin and a PCSK9 inhibitor can be considered to ensure early and rapid attainment of the LDL-C goal [1]. These Chinese recommendations align broadly with international guidelines such as the ESC/EAS 2019 dyslipidemia guidelines (with 2025 focused update maintaining aggressive LDL-C targets: <55 mg/dL [<1.4 mmol/L] for very-high-risk and <70 mg/dL [<1.8 mmol/L] for high-risk patients), but allow earlier PCSK9 inhibitor initiation in ultra-high-risk Chinese patients to address local tolerability and risk profiles. Studies have shown that early initiation of PCSK9 monoclonal antibodies can lead to earlier and more significant reductions in ASCVD risk, and long-term use (≥7 years) demonstrates a favorable safety profile [21].

The approved PCSK9 inhibitors in China are evolocumab, alirocumab, tafolecimab, and the small interfering RNA inclisiran. Table 1 summarizes key characteristics of these approved agents for rapid clinical reference. Evolocumab 140 mg or alirocumab 75 mg subcutaneously once every two weeks has a favorable safety and tolerability profile. They can reduce LDL-C levels by 50% to 70% significantly. The incidence of adverse events including serious adverse events, muscle events, new onset diabetes, hemorrhagic stroke and neurocognitive events is similar to that observed with placebo. Subcutaneous administration of tafolecimab 150 mg every two weeks is comparable in magnitude of LDL-C reduction with similar safety in Chinese populations. Inclisiran has similar efficacy in reducing LDL-C to PCSK9 monoclonal antibodies but has a longer duration of action; efficacy is

maintained for approximately 6 months after a single injection. The most common adverse reactions are pain or induration at the injection site, fatigue, nausea, and muscle pain [46]. Overall, these agents have demonstrated excellent long-term safety in major trials with no significant increase in serious AEs vs. placebo.

Table 1. Characteristics of overseas injectable PCSK9 inhibitors for lipid lowering

Drug	Company	Indication	Dosage Form	Dosing Frequency	Average LDL-C Reduction
Evolocumab	Amgen	Primary hypercholesterolemia/mixed dyslipidemia in adults; Reducing cardiovascular event risk in ASCVD; Adjuvant therapy for HoFH in adults/adolescents (≥12 years)	Subcutaneous Injection	140mg every 2 weeks; 420mg monthly (420mg monthly recommended for HoFH)	68.08%~ 75%
Inclisiran	Novartis	Primary hypercholesterolemia (including HeFH)/mixed dyslipidemia in adults	Subcutaneous Injection	1 injection at month 0 and month 3, then every 6 months thereafter	47.0%~ 65.0%
Alirocumab	Sanofi	Primary hypercholesterolemia (including HeFH)/mixed dyslipidemia in adults	Subcutaneous Injection	150mg every 2 weeks	54.7%~ 63.3%

5. Conclusions

PCSK9 inhibitors have revolutionized ASCVD management, and represent a cornerstone of modern pharmacotherapy for LDL-C lowering and risk reduction. This therapeutic class, now represented by monoclonal antibodies, has been validated in clinical practice and has demonstrated a significant incremental LDL-C reduction when administered as adjunctive treatment to standard lipid-lowering regimens including statins. Large randomized controlled outcome trials have convincingly demonstrated the ability of evolocumab and alirocumab to reduce the incidence of major adverse cardiovascular events. As a result, the drugs are incorporated in international guidelines for secondary prevention in high-risk groups, including patients with familial hypercholesterolemia and established ASCVD.

The advent of siRNA-based agents such as inclisiran has introduced a new paradigm of sustained PCSK9 expression suppression, with the potential to provide extended dosing intervals that may help overcome long-term adherence challenges while maintaining a well-established safety profile.

Contemporary scientific work is expanding the scope of PCSK9 inhibition via novel modalities including genome-editing platforms, orally bioavailable small-molecule inhibitors, peptide-derived agents and therapeutic vaccines, that are in preclinical and early-phase clinical development. Late-stage oral PCSK9 inhibitors (e.g., enlicitide decanoate) have shown antibody-like efficacy in Phase 3 trials (e.g., ~55–60% LDL-C reductions with favorable safety), and gene-editing candidates (VERVE-102) have demonstrated durable ~50–70% LDL-C reductions in Phase 1b data, positioning the field for a move toward more convenient, potentially one-time therapies that could radically improve access and patient outcomes.

Nevertheless, several challenges are still ahead before clinical implementation. These include high cost of therapy and barriers to access (particularly in Asia and resource-limited settings), adherence challenges with current agents given chronic parenteral administration, the need for more long-term safety data (including potential off-target effects with genome-editing approaches), and definitive evidence in primary prevention populations. Future studies should focus on real-world evidence, cost-

effectiveness, combination strategies, and broader investigations in different populations to optimize therapeutic strategies, improve global accessibility, and extend benefits to wider patient populations. Ongoing trials and innovations hold the potential to improve the efficacy, convenience, and equity of lipid management and, if cost, access, and long-term safety issues are proactively addressed, will contribute to a significant reduction in the global burden of ASCVD.

References

[1] Wang ZW, et al. Chinese Guidelines for the Management of Blood Lipids (2023). Chinese Circulation Journal. 2023;38(3):237-271.

[2] Banach, M., et al., Statin intolerance - an attempt at a unified definition. Position paper from an International Lipid Expert Panel. Expert Opin Drug Saf, 2015. 14(6): p. 935–55.

[3] Guan, Y., et al., PCSK9 Promotes LDLR Degradation by Preventing SNX17-Mediated LDLR Recycling. Circulation, 2025. 151(21): p. 1512–1526.

[4] Wang, Y., et al., Molecular characterization of proprotein convertase subtilisin/kexin type 9-mediated degradation of the LDLR. J Lipid Res, 2012. 53(9): p. 1932–43.

[5] Lin, Z., et al., PCSK9 E670G polymorphism increases risk of coronary artery disease in a Chinese Han population. J Int Med Res, 2024. 52(10): p. 300060519892177.

[6] Cohen, J.C., et al., Sequence variations in PCSK9, low LDL, and protection against coronary heart disease. N Engl J Med, 2006. 354(12): p. 1264–72.

[7] Giunzioni, I., et al., Local effects of human PCSK9 on the atherosclerotic lesion. J Pathol, 2016. 238(1): p. 52–62.

[8] Ferri, N., et al., Proprotein convertase subtilisin kexin type 9 (PCSK9) secreted by cultured smooth muscle cells reduces macrophages LDLR levels. Atherosclerosis, 2012. 220(2): p. 381–6.

[9] Ding, Z., et al., Hemodynamic shear stress via ROS modulates PCSK9 expression in human vascular endothelial and smooth muscle cells and along the mouse aorta. Antioxid Redox Signal, 2015. 22(9): p. 760–71.

[10] Tang, Z.H., et al., new role of PCSK9 in atherosclerotic inflammation promotion involving the TLR4/NF-kappaB pathway. Atherosclerosis, 2017. 262: p. 113–122.

[11] Ragusa, R., et al., PCSK9 and coronary atherosclerosis progression beyond LDL-cholesterol in coronary artery disease patients. Eur J Clin Invest, 2025. 55(11): p. e70083.

[12] Correction to: PCSK9 (Proprotein Convertase Subtilisin/Kexin 9) Enhances Platelet Activation, Thrombosis, and Myocardial Infarct Expansion by Binding to Platelet CD36. Circulation, 2021. 143(1): p. e4.

[13] Paciullo, F., et al., Pleiotropic effects of PCSK9-inhibition on hemostasis: Anti-PCSK9 reduce FVIII levels by enhancing LRP1 expression. Thromb Res, 2022. 213: p. 170–172.

[14] Schwartz, G.G., et al., Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome. N Engl J Med, 2018. 379(22): p. 2097–2107.

[15] Zahger, D., et al., Triglyceride Levels, Alirocumab Treatment, and Cardiovascular Outcomes After an Acute Coronary Syndrome. J Am Coll Cardiol, 2024. 84(11): p. 994–1006.

[16] White, H.D., et al., Alirocumab after acute coronary syndrome in patients with a history of heart failure. Eur Heart J, 2022. 43(16): p. 1554–1565.

[17] Raber, L., et al., Effect of Alirocumab Added to High-Intensity Statin Therapy on Coronary Atherosclerosis in Patients with Acute Myocardial Infarction: The PACMAN-AMI Randomized Clinical Trial. JAMA, 2022. 327(18): p. 1771–1781.

[18] Blom, D.J., et al., Efficacy and Safety of Alirocumab in Adults with Homozygous Familial Hypercholesterolemia: The ODYSSEY HoFH Trial. J Am Coll Cardiol, 2020. 76(2): p. 131–142.

[19] Catapano, A.L., et al., 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias. Rev Esp Cardiol (Engl Ed), 2017. 70(2): p. 115.

[20] Hadjiphilippou, S. and K.K. Ray, Evolocumab and clinical outcomes in patients with cardiovascular disease. J R Coll Physicians Edinb, 2017. 47(2): p. 153–155.

[21] O'Donoghue, M.L., et al., Long-Term Evolocumab in Patients with Established Atherosclerotic Cardiovascular Disease. Circulation, 2022. 146(15): p. 1109–1119.

[22] Hochholzer, W. and F.J. Neumann, [The new 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation]. Dtsch Med Wochenschr, 2016. 141(11): p. 782–5.

[23] Cholesterol Treatment Trialists, C., et al., Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet, 2010. 376(9753): p. 1670–81.

[24] Koskinas, K.C., et al., Evolocumab for Early Reduction of LDL Cholesterol Levels in Patients with Acute Coronary Syndromes (EVOPACS). J Am Coll Cardiol, 2019. 74(20): p. 2452–2462.

[25] Lancellotti, P. and C. Oury, A Highly Durable RNAi Therapeutic Inhibitor of PCSK9. N Engl J Med, 2017. 376(18): p. e38.

[26] 26. Ray, K.K., et al., Inclisiran in Patients at High Cardiovascular Risk with Elevated LDL Cholesterol. N Engl J Med, 2017. 376(15): p. 1430–1440.

[27] Nishikido, T. and K.K. Ray, Inclisiran for the treatment of dyslipidemia. Expert Opin Investig Drugs, 2018. 27(3): p. 287–294.

[28] Wright, R.S., et al., Effects of Inclisiran in Patients with Atherosclerotic Cardiovascular Disease: A Pooled Analysis of the ORION-10 and ORION-11 Randomized Trials. Mayo Clin Proc, 2024.

[29] Raal, F.J., et al., Inclisiran for the Treatment of Heterozygous Familial Hypercholesterolemia. N Engl J Med, 2020. 382(16): p. 1520–1530.

[30] Ray, K.K., et al., Long-term efficacy and safety of inclisiran in patients with high cardiovascular risk and elevated LDL cholesterol (ORION-3): results from the 4-year open-label extension of the ORION-1 trial. Lancet Diabetes Endocrinol, 2023. 11(2): p. 109–119.

[31] Leiter, L.A., et al., Inclisiran in individuals with diabetes or obesity: Post hoc pooled analyses of ORION-9, ORION-10 and ORION-11 Phase 3 randomized trials. Diabetes Obes Metab, 2024. 26(8): p. 3223–3237.

[32] Johns, D.G., et al., Orally Bioavailable Macrocyclic Peptide That Inhibits Binding of PCSK9 to the Low-Density Lipoprotein Receptor. Circulation, 2023. 148(2): p. 144–158.

[33] Ballantyne, C.M., et al., Phase 2b Randomized Trial of the Oral PCSK9 Inhibitor MK-0616. J Am Coll Cardiol, 2023. 81(16): p. 1553–1564.

[34] Ballantyne, C.M., et al., Efficacy and Safety of Oral PCSK9 Inhibitor Enlicitide in Adults with Heterozygous Familial Hypercholesterolemia: A Randomized Clinical Trial. JAMA, 2026. 335(2): p. 129–139.

[35] Koren, M.J., et al., An Oral PCSK9 Inhibitor for Treatment of Hypercholesterolemia: The PURSUIT Randomized Trial. J Am Coll Cardiol, 2025. 85(21): p. 1996–2007.

[36] Toth, S., D. Pella, and J. Fedacko, Vaccines Targeting PSCK9 for the Treatment of Hyperlipidemia. Cardiol Ther, 2020. 9(2): p. 323–332.

[37] Landlinger, C., et al., The AT04A vaccine against proprotein convertase subtilisin/kexin type 9 reduces total cholesterol, vascular inflammation, and atherosclerosis in APOE*3Leiden.CETP mice. Eur Heart J, 2017. 38(32): p. 2499–2507.

[38] Galabova, G., et al., Peptide-based anti-PCSK9 vaccines - an approach for long-term LDLc management. PLoS One, 2014. 9(12): p. e114469.

[39] Momtazi-Borojeni, A.A., et al., Long-term generation of antiPCSK9 antibody using a nanoliposome-based vaccine delivery system. Atherosclerosis, 2019. 283: p. 69–78.

[40] Zeitlinger, M., et al., A phase I study assessing the safety, tolerability, immunogenicity, and low-density lipoprotein cholesterol-lowering activity of immunotherapeutics targeting PCSK9. Eur J Clin Pharmacol, 2021. 77(10): p. 1473–1484.

[41] Ding, Q., et al., Permanent alteration of PCSK9 with in vivo CRISPR-Cas9 genome editing. Circ Res, 2014. 115(5): p. 488–92.

[42] Hooper, A.J., X.L. Tang, and J.R. Burnett, VERVE-101, a CRISPR base-editing therapy designed to permanently inactivate hepatic PCSK9 and reduce LDL-cholesterol. Expert Opin Investig Drugs, 2024. 33(8): p. 753–756.

[43] Vafai, S., et al., abstract 4139206: Design of Heart-2: a phase 1b clinical trial of VERVE-102, an in vivo base editing medicine delivered by a GalNAc-LNP and targeting PCSK9 to durably lower LDL cholesterol. Circulation, 2024. 150(Suppl_1): p. A4139206–A4139206.

[44] Lee, R.G., et al., Efficacy and Safety of an Investigational Single-Course CRISPR Base-Editing Therapy Targeting PCSK9 in Nonhuman Primate and Mouse Models. Circulation, 2023. 147(3): p. 242–253.

[45] Zhou Y. Expert consensus on medication therapy management pathway for patients with coronary atherosclerotic heart disease[J]. Journal of Clinical Medication Therapy, 2023, 21(06): 1-18.

[46] Wang Z W, Guo Y L. Chinese guidelines for lipid management (primary care version, 2024)[J]. Chinese Circulation Journal, 2024, 39(04): 313-321.