REVIEW ARTICLE

The Role of PCSK9 Inhibition and Small Interference RNA (siRNA) in The Management of Dyslipidaemia and ASCVD

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Abstract

Compelling evidence linking low-density lipoprotein cholesterol (LDL-C) reduction to decreased mortality has positioned LDL-C lowering as a central strategy in the prevention of atherosclerotic cardiovascular disease (ASCVD). Nonetheless, despite widespread statin use, an estimated 10–20% of individuals at high or very high cardiovascular risk fail to attain guideline-recommended LDL-C targets. This persistent treatment gap underscores the need for more potent and durable lipid-lowering strategies, particularly among patients with familial hypercholesterolemia (FH) and those with established ASCVD whose LDL-C levels remain inadequately controlled despite optimized combination therapy, including statins, ezetimibe, and proprotein convertase subtilisin–kexin type 9 (PCSK9) monoclonal antibodies. Inclisiran, a first-in-class small interfering RNA agent, addresses this unmet need by selectively inhibiting hepatic synthesis of PCSK9, thereby enhancing low-density lipoprotein receptor (LDLR) recycling and accelerating LDL-C clearance. Nevertheless, thus far, no cardiovascular outcome trial (CVOT) has been available. With a convenient twice-yearly dosing regimen, inclisiran consistently achieves LDL-C reductions exceeding 50% and demonstrates a favourable tolerability profile, offering an effective and patient-friendly advancement in dyslipidaemia management.

KEYWORDS: dyslipidaemia, ASCVD, PCSK9 inhibition, siRNA, inclisiran

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Introduction

A foremost significant atherosclerotic cardiovascular disease (ASCVD) risk factor is hypercholesterolemia.(1) Statin use is robustly recommended as the first-line treatment for ASCVD management since it has considerably reduced the cardiovascular disease (CVD) events globally. Robust evidence indicates that both low and extremely low low-density lipoprotein cholesterol (LDL-C) concentrations are safe and well tolerated.(2,3) Despite the widespread availability of effective and safe cholesterol-lowering therapies, LDL-C levels remain above optimal targets in the majority of the population. In spite of statins, other LDL-C–lowering medications remain necessary, as some patients experience serious statin-related adverse effects, and others cannot achieve sufficient LDL-C reduction due to extremely high baseline levels or very high CVD risk.(4)

After proprotein convertase subtilisin–kexin type 9 (PCSK9) gene mutations were identified as associated with autosomal dominant hypercholesterolemia (ADH), the role of PCSK9 in cholesterol regulation has been established. (5) PCSK9 binds to LDLR and enables its degradation (6), leading to a rise in LDL-C and suggesting significant therapeutic potential. Therefore, over the past few years, human studies have assessed the ability to reduce LDL-C levels by inhibiting PCSK9 with monoclonal antibodies.(7,8) According to a meta-analysis, the monoclonal antibodies,

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namely evolocumab and alirocumab, are both well-tolerated and safe medications that significantly lowered LDL-C levels by more than 50%, increased HDL-C levels, and resulted in satisfactory changes in other lipids.(9)

Despite high-intensity statin therapy, LDL-C targets are not achieved in 10–20% of patients with high or very high ASCVD risk, underscoring the urgent need for more effective strategies to manage hypercholesterolemia.(10) Statin use varies across Asian countries, including Indonesia due to differences in healthcare policies and economic factors. A previous study found that many patients do not follow their treatment schedule: 50.4% stopped taking their medication once their cholesterol levels improved, and 56.3% sometimes forgot to take their pill. Additionally, 65.1% believed that missing a dose would not affect their cholesterol levels.(11,12) Several adverse effects, including myalgia and rare instances of rhabdomyolysis, have been reported with statin therapy and may necessitate discontinuation. Furthermore, although PCSK9 inhibitors (PCSK9i) enable most patients to achieve LDL-C targets, a subset of individuals appears to respond inadequately, largely due to poor adherence, incorrect administration, and dermatological conditions that interfere with drug absorption.(13,14) A novel cholesterol-lowering therapy using small interfering RNAs (siRNAs) has been developed to circumvent the drawbacks of statins and PCSK9i.

This narrative review provides an overview of PCSK9's role in cholesterol metabolism, its pleiotropic and clinical implications, and the clinical impact of PCSK9 silencing, with a special focus on inclisiran. The relevant literatures were collected through PubMed, Scopus, Embase, and Web of Science, including articles published from 2001 to 2026. The search used combinations of MeSH terms and keywords with Boolean operators (AND/OR): "statin", "dyslipidaemia", "LDL-C", "atherosclerosis-cardiovascular disease (ASCVD)", "cardiovascular disease (CVD)", "PCSK9 inhibitors", "PCSK9 monoclonal antibodies", "small-interfering RNA", "inclisiran", "safety", "efficacy" and "ORION trials". Eligible studies were reviews articles, observational studies, randomized clinical trials (RCTs), meta-analysis, and real-world observational studies.

Function of PCSK9 in Cholesterol Metabolism

LDL-C particles arise from the maturation of circulating lipoproteins and are rich in cholesterol, contain relatively slight triglyceride, and include apolipoprotein B-100, which mediates binding to LDLR. Diminished LDLR availability on hepatocyte membranes leads to elevated plasma LDL-C and contributes to ASCVD development.(14,15)

After internalization, the LDL-C–LDLR complex is processed via the endosomal–lysosomal pathway, where LDL particles are dismantled into cholesterol and triglycerides before being released into the cytosol.(16) LDLR, in turn, may either be recycled back to the cell surface or targeted for degradation.(17) Over the past decade, elevated plasma LDL-C levels have been shown to correlate with increased circulating PCSK9 concentrations, which regulate the lifespan of LDLR.(18) Active PCSK9 binds to LDLR and directs them toward lysosomal degradation, thereby preventing their normal recycling. This reduction in cell-surface LDLR density results in higher LDL-C levels.(19,20) Instead, inhibition of PCSK9 enhances both the recycling and surface expression of LDLR, thereby increasing LDL-C clearance from circulation and markedly lowering plasma LDL-C.(17)

PCSK9's Pleiotropic Effects

Beyond its role in controlling plasma LDL-C levels, PCSK9 has been shown in preclinical studies to exert pleiotropic effects that contribute to the development of atherosclerosis. Endothelial cells (21), vascular smooth muscle cells (VSMCs) (22), and macrophages (23) are three cell types involved in atherosclerosis that express PCSK9. Overexpression results in its accumulation in the arterial wall, independent of plasma lipid and lipoprotein levels, thereby directly modulating the size and composition of atherosclerotic plaques.(24) Experimental mouse models with either wild-type or gain-of-function PCSK9 overexpression demonstrate increased atherosclerotic plaque size.(25,26) Furthermore, PCSK9 affects the metabolism of triglyceride-rich lipoproteins, which are highly atherogenic and closely linked to atherosclerosis development and progression.(27) These findings may elucidate the mechanisms through which pharmacological PCSK9 antagonism confers protection against ASCVD.(28)

Previous genetic studies have shown that *PCSK9* is essential for preserving cholesterol homeostasis. Gain-of-function mutations in the P*CSK9* gene enhance atherosclerosis development and increase the risk of ASCVD events.(18) Furthermore, *PCSK9* gene, specifically the *E670G* (rs505151) gain-of-function variant, was genotyped and the results demonstrated that it was associated with

major adverse cardio-cerebrovascular events (MACCE) in ST-elevation myocardial infarction (STEMI) at 6-month follow-up.(29) Conversely, the incidence of coronary heart disease (CHD) over a 15-year period, including myocardial infarction, fatal CHD, or coronary revascularization, were compared; they discovered that sequence variants (loss-of-function) in the *PCSK9* gene associated with lower LDL-C conferred protection against CHD.(30) The inflammatory response and endothelial dysfunction appear to be affected by *PCSK9*. As monocyte-derived macrophages contribute to a local pro-inflammatory milieu, monocyte migration is a critical step in the formation of atherosclerotic lesions. (31,32)

Lipoprotein-associated phospholipase A_2 (Lp-PLA_2) is an enzyme that hydrolyzes, modified and oxidized phospholipids on the surface of LDL-C, thereby contributing to endothelial dysfunction and inflammatory processes within atherosclerotic plaques. Lp-PLA_2 is primarily produced by macrophages, T lymphocytes, and monocytes. (33) In obese individuals, circulating Lp-PLA_2 levels have been shown to correlate significantly with oxidized LDL-C. (34) As previously discussed, oxidized LDL-C within sub-endothelial space-driven by locally generated reactive oxygen species-plays a pivotal role in atherogenesis.(35) In addition, human PCSK9 promotes monocyte recruitment into atherosclerotic lesions and their differentiation into macrophage, leading to alterations in plaque composition and morphology.(36)

Higher circulating PCSK9 concentrations correlate with greater carotid intima–media thickness, independent of traditional CVD risk factors, including sex, hypertension, smoking, lipid levels, obesity, and inflammatory biomarkers. (37,38) In addition, PCSK9 concentrations exhibit a linear association with a greater necrotic core proportion within atherosclerotic plaques.(39) Accordingly, inhibition of PCSK9 in cultured vascular smooth muscle cells and in animal models significantly reduces vascular cell adhesion molecule-1 expression, thereby limiting monocyte recruitment into atherosclerotic lesions.(40) As shown in Figure 1, PCSK9 inhibition influences several key cell types involved in atherosclerotic progression. Importantly, PCSK9 functions extend beyond lipid homeostasis, and its inhibition may yield pleiotropic protective effects in patients at elevated ASCVD risk.(41)

Inhibition of PCSK9

The first indication of PCSK9 inhibition's potential therapeutic value was initially seen in two French families with ADH.(5) Gain-of-function mutations in PCSK9 are linked to a higher risk of ASCVD, according to observational cohort and linkage studies.(42,43) Targeted inhibition of PCSK9 has emerged as a novel therapeutic strategy for reducing ASCVD risk. By increasing hepatic LDLR expression, this approach enhances the clearance of circulating LDL-C.

Monoclonal antibodies called evolocumab, alirocumab, and bococizumab bind to PCSK9 and prevent it from interacting with LDLR. Whether used alone or in conjunction with statins, PCSK9i has recently become a great therapeutic option for lowering LDL-C.(44) PCSK9i provides strong LDL-C reduction. A comprehensive meta-analysis encompassing 71 randomized, placebo-controlled trials revealed that PCSK9 inhibition was associated with a 50.7% reduction in LDL-C relative to placebo.(45) Every

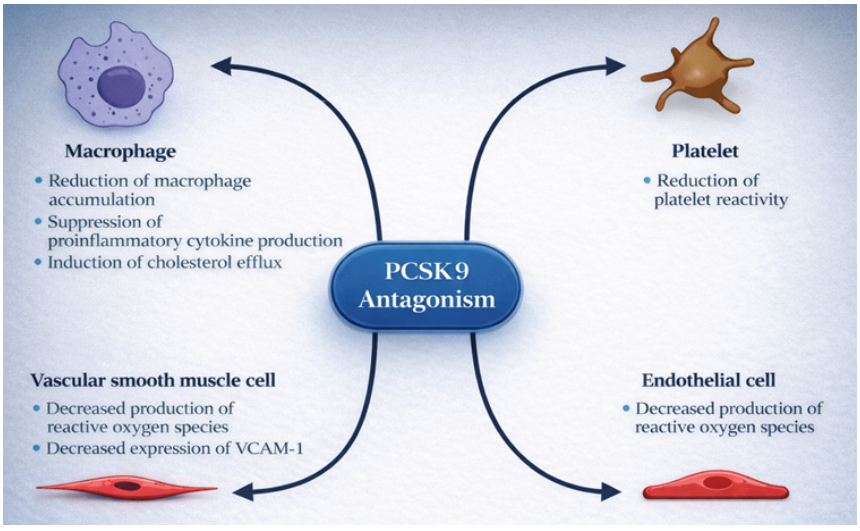

Figure 1. Impact of PCSK9 inhibition on the primary cellular components involved in the progression of atherosclerosis. VCAM-1: vascular cell adhesion molecule 1.

2-4 weeks, PCSK9i must be injected subcutaneously.(46) The requirement for relatively frequent subcutaneous injections reduces patient's adherence to medication and, as a result, the therapeutic benefits (13), with injection-site and allergic reaction rates comparable to those seen with placebo (46).

Another strategy for PCSK9 inhibition utilizes siRNAs. These short RNA molecules, typically 20–30 nucleotides long, inhibit the translation of PCSK9 messenger RNA into protein.(47) Small interfering RNAs act in a selective, catalytic manner by forming effector RNA-induced silencing complexes that mediate sequence-specific silencing of their complementary target mRNAs. (48,49)

SiRNAs Therapeutics: A Potential New Class

Therapeutics based on RNA interference provide an effective strategy for identifying potent, targeted inhibitors of disease targets across diverse molecular classes. siRNAs are a core cellular mechanism responsible for gene expression silencing (50,51), hence can be utilized in the development of novel therapeutics. siRNA therapy induces enzymatic cleavage of target mRNA, thereby decreasing protein expression through a highly specific mechanism that harnesses the natural RNA interference pathway with predictable efficacy and duration.

The enzyme Dicer processes long double-stranded RNA (dsRNA) into siRNAs. These siRNAs are integrated into the strand-separating RNA-induced silencing complex (RISC). The guide (antisense) strand within the RISC recognizes and binds complementary mRNA sequences. Argonaute, the catalytic component of RISC responsible for mRNA degradation, thereby cleaves the target mRNA and downregulates its expression (50), as illustrated in Figure 2.

Inclisiran: Mechanism of Action

Inclisiran consist of two RNA strands, the guide and passenger. Given the inherent instability and limited cellular permeability of siRNAs, multiple chemical modifications have been introduced to enhance their resistance to degradation and to optimize delivery to target tissues. Specifically, the duplex RNA includes one 2′-deoxy nucleotide, eleven 2′-fluoro nucleotides, and thirty-two 2′-O-methyl–modified nucleotides.(51)

The RNA strands incorporate thiophosphodiester linkages at their unconjugated terminal nucleotides, while the passenger strand is modified at the 3′ end with a triantennary N-acetylgalactosamine (GalNAc) conjugate.(52) GalNAc serves as a high-affinity ligand for the asialoglycoprotein receptor (ASGPR) expressed on hepatocytes. Comparative studies using primary mouse hepatocyte cultures demonstrated that GalNAc conjugation markedly enhances siRNA uptake, whereas unconjugated siRNA is taken up a minimal or negligible extent.(53)

Consequently, inclisiran exerts its effects through RNA interference, wherein double-stranded RNA leads to targeted gene silencing by degrading complementary mRNA.(54) After inclisiran is taken up by hepatocytes via interaction with the asialoglycoprotein receptor, the guide strand is incorporated into the RISC. The guide strand-RISC complex then attaches to PCSK9 mRNA and promotes its degradation, thereby preventing the synthesis of PCSK9 protein. Figure 3 presents the proposed mechanism.

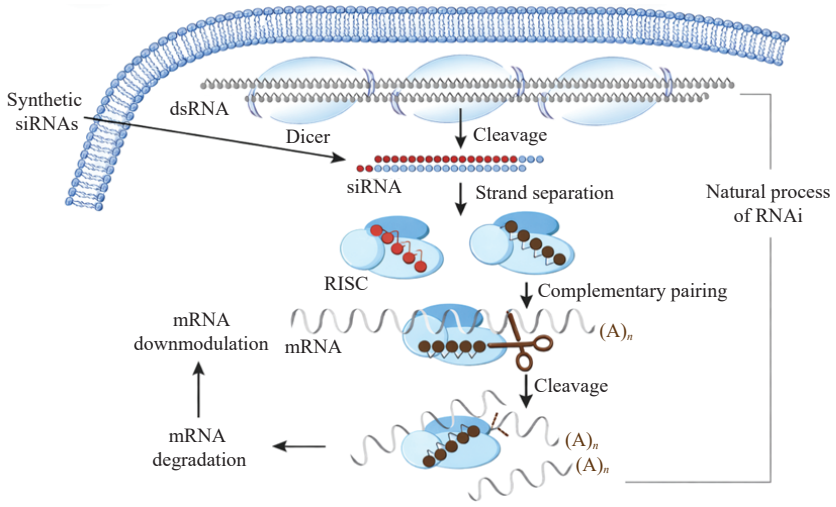

Figure 2. Cellular mechanism of siRNA-mediated RNA interference and mRNA degradation.

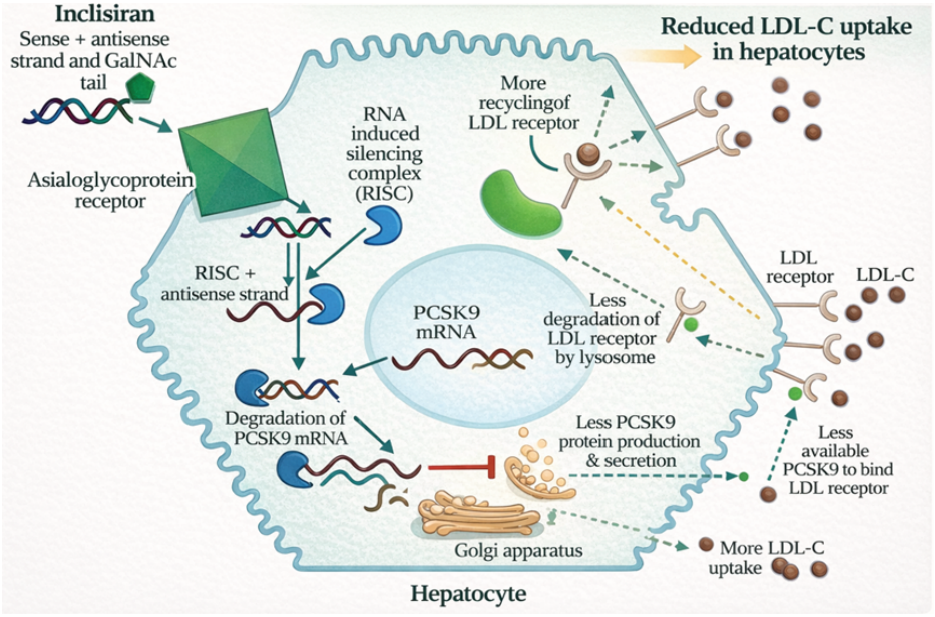

Figure 3. Inclisiran mechanism of action: RISC-mediated PCSK9 suppression and increased LDL-C clearance.

Efficacy, Pharmacodynamic Properties and Safety of Inclisiran

The safety and efficacy of inclisiran were first demonstrated in a phase-1 randomized, single-blind, placebo-controlled trial. Healthy participants with baseline LDL-C levels of at least 100 mg/dL were randomized in a 3:1 ratio to receive either subcutaneous inclisiran or a placebo. The trial utilized both single-ascending-dose cohorts (ranging from 25, 100, 300 500, or 800 mg) and multiple-dose regimens (weekly, bi-weekly, or monthly), administered with or without concurrent statin therapy. Single-dose administration of inclisiran demonstrated that doses of 300 mg or above achieved up to a 74.5% reduction in PCSK9 by day 84, while LDL-C reductions of up to 50.6% were observed with doses of 100 mg or higher. The treatment was well tolerated, and sustained reductions in PCSK9 and LDL-C persisted for at least six months with doses ≥300 mg.(41,55)

Hypercholesterolemia and ASCVD frequently coexist with comorbidities such as diabetes mellitus and chronic renal disease. Animal studies in rats and cynomolgus macaques demonstrated that subcutaneous inclisiran administration had no adverse effects on renal function. (56) Correspondingly, clinical trial data showed that inclisiran has comparable safety and pharmacodynamic profiles in patients with preserved or impaired renal function, eliminating the need for dose modification.(57) Furthermore, baseline diabetes mellitus did not diminish the lipid-lowering efficacy of inclisiran.(58) Comparison between PCSK9i and inclisiran is presented in Table 1.

ORION Clinical Trials

To thoroughly investigate the safety and potential efficacy of inclisiran, some investigators launched the ORION clinical development program. Within this framework, the ORION-1 served as phase 2, double-blind, randomized trial designed to test multiple ascending dose in patients with high LDL-C. These subjects were already on optimized lipid-lowering regimens, such as ezetimibe and the highest tolerable doses of statins. One-year follow-up results demonstrated that inclisiran produced sustained and durable reductions in both LDL-C and PCSK9 levels. The greatest reductions in LDL-C (29.9%–46.4%) and PCSK9 (53.1%–60.5%) were observed with a two-dose regimen administered on days 1 and 90. These findings indicate that a 300 mg dose is the most effective, supporting a potential dosing interval of once every six months.(59,60)

The 18 month ORION 10 and ORION 11 phase-3 clinical trials evaluated inclisiran in a high-risk ASCVD population with elevated LDL-C. These randomized, placebo-controlled studies were designed to assess the efficacy and safety profile through a parallel-group comparison over 1.5 years of observation. In both studies, biannual administration of inclisiran led to LDL-C reductions of approximately 50%. Finally, these studies confirmed that PCSK9 levels were reduced by 69.8% in ORION 10 and by 63.9% in ORION 11 at 18 months of follow-up. Compared with placebo, inclisiran also significantly lowered total cholesterol, apolipoprotein B, non-HDL cholesterol, triglycerides, and lipoprotein(a),

Table 1. Comparison between PCSK9i and inclisiran.

Domain	PCSK9 Inhibitors (Evolocumab and Alirocumab)	Small Interfering RNA (Inclisiran)
Mechanism	• Fully human monoclonal Ab bind circulating PCSK9 protein • Preventing LDL-R degradation → increased LDL-R recycling → ↓ LDL-C	• siRNA targeting hepatic PCSK9 mRNA • siRNA → intracellular degradation via RISC complex → ↓ PCSK9 synthesis
Level of action	• Extracellular (neutralizes circulating PCSK9)	• Intracellular (hepatic gene silencing)
Dosing regimen	• Injection sc every 2 weeks	• Injection sc day-1 →day-90 →every 6 months
Adherence implication	• Higher burden → self-administration required frequently	• Favourable → twice-yearly maintenance dosing • Improve adherence
LDL-C reduction	• ~50-65% reduction	• ~45-52% reduction (slightly lower but still comparable)
Effect on other lipid	• ↓ ApoB, ↓ Lp(a), ↓ modest TG	• ↓ ApoB, ↓ Lp(a), slight ↑ HDL-C
Clinical outcomes	• Robust CVOT evidence • ↓ MACE (CV death, myocardial infarction, stroke, hospitalization for unstable angina and coronary revascularization)	• Emerging evidence → ongoing CVOT trial (ORION-4 study) • Early signs suggest ↓ MACE but not yet definitive
Safety profile	• Well established; injection-site reaction • Rare neurocognitive issue	• Very favourable, mostly injection-site reaction

while increasing HDL cholesterol. Adverse events were generally mild to moderate and occurred at similar rates in the inclisiran and placebo groups.(61) Among Asian patients with established ASCVD or at high risk for ASCVD, inclisiran demonstrated robust LDL-C–lowering efficacy with a favourable safety profile. In the phase 3, randomized, double-blind ORION-18 trial, participants were assigned in a 1:1 ratio to receive inclisiran sodium 300 mg or placebo on days 1, 90, and 270. At day 330, a ≥50% reduction in LDL-C was achieved in 71.7% of patients treated with inclisiran, compared with 1.5% in the placebo group.(62) In the extension study over 4 years, biannual administration of inclisiran produced persistent LDL-C and PCSK9 lowering and was well tolerated.(63)

It remains uncertain whether LDL-C lowering with inclisiran reduces major adverse cardiovascular events (MACE), pending the results from the cardiovascular outcome trial (CVOT). Accordingly, a pooled analysis of the ORION-9, -10, and -11 trials was conducted, which comprised patients with FH, ASCVD, and ASCVD risk equivalent on high-intensity statins. This study provides preliminary evidence of the potential CVD benefits of LDL-C reduction with inclisiran and suggests a possible decrease in MACE. However, a larger CVOT is needed to confirm these findings.(64)

Homozygous familial hypercholesterolemia (HoFH) represents one of the most life-threatening manifestations of lifelong LDL-C exposure, with markedly elevated concentrations present from birth and leading to premature ASCVD and sudden cardiac death if left inadequately treated.(65,66) For all the surrounding novel lipid-lowering agents, lipoprotein apheresis remains the only intervention with convincing evidence of long-term clinical benefit in this population at that time.(67,68) The ORION-5 trial underscored this reality: despite achieving profound suppression of circulating PCSK9, failed to deliver any meaningful reduction in LDL-C in adults with HoFH. (69) This discordance between biomarker modulation and clinical efficacy exposes a persistent fallacy in lipid therapeutics, the assumption that PCSK9 inhibition is universally effective. Individuals with HoFH demonstrate a high degree of genetic variability. The efficacy of LDL-C lowering therapy is substantially affected by sequence variations in the LDLR gene, with the poorest therapeutic response reported in those with the homozygous LDLR genotype, particularly with null/null variants.(70) Yet, the more encouraging response observed in adolescents with HoFH, where inclisiran was both effective and well tolerated over one year, suggests that disease biology, residual LDLR function, and timing of intervention may be as critical as the drug itself.(71)

By contrast, the ORION-9 trial demonstrated that inclisiran produced a robust, clinically meaningful reduction in LDL-C relative to placebo, while maintaining a favourable safety profile in adults with HeFH.(72) Consistent efficacy was also observed in adolescents with HeFH, in whom LDL-C lowering was sustained for up to two years and the therapy was well tolerated.(73) Taken together, these findings suggest that inclisiran is a potentially game-changing intervention, offering durable lipid control with acceptable tolerability, particularly in patients burdened by multiple comorbidities (Table 2).

Table 2. Summary of ORION clinical trials.

Study	Study Design	Population	Primary Outcomes	Follow-up	Results	Ref.
ORION-1	• RCT phase-2, multi-centre, double-blind, placebo-control, multiple ascending dose trial • Single dose of placebo or 200, 300, 500 mg inclisiran • Two doses of placebo or 100, 200, 300 mg inclisiran	• 501 patients at high-risk for CVD with elevated LDL-C	Mean percentage change from baseline LDL-C at 180 days.	Day 180	LDL-C reduction of 52.6% (p<0.001 *vs* placebo)	60
ORION-3	• RCT phase 2 extension of ORION-1 • 4-year open-label extension study	• 497 patients with prevalent ASCVD or high-risk primary prevention and elevated LDL-C	Mean percentage change in LDL-C from the start of ORION-1 trial	Day 1440 (4 years)	LDL-C reduction of 44.2%	63
ORION-5	• RCT phase-3, 2-part multi-centre study • Part-1: 6 months double-blind, placebo control • Part-2: 18 months open label, single-arm (placebo arm switch to inclisiran on day 180) • All patients received inclisiran 270, 450, and 630 mg sc and end of study	• 56 patients with HoFH and elevated LDL-C • Inclisiran (n=37) and placebo (n=19)	Mean percentage change from baseline LDL-C	Day 720	This study did not show a statistically LDL-C reduction compared with placebo	69
ORION-9	• RCT phase-3, double blind in 1:1 ratio • Inj. sc inclisiran and placebo control 300 mg (day-1, day-90 then every six month) • Placebo (240) and inclisiran (242)	• 482 adults with HeFH	Mean percentage change from baseline LDL-C	Day 510	LDL-C reduction of 39.7% (p<0.001 *vs* placebo)	72
ORION-10	• RCT phase-3, double blind in 1:1 ratio • Inj. sc inclisiran and placebo control 300 mg (day-1, day-90 then every six months) • Placebo (780) and inclisiran (781)	• 1561 patients with ASCVD and elevated LDL-C	Mean percentage change from baseline LDL-C	Day 510	LDL-C reduction of 52.3% (p<0.001 *vs* placebo)	61
ORION-11	• RCT phase-3, double blind in 1:1 ratio • Inj. sc inclisiran and placebo control 300 mg (day-1, day-90 then every six month) • Placebo (807) and inclisiran (810)	• 1617 patients with ASCVD risk equivalent and elevated LDL-C	Mean percentage change from baseline LDL-C	Day 510	LDL-C reduction of 49.9% (p<0.001 *vs* placebo)	61
ORION-18	• RCT phase-3, double blind in 1:1 ratio • Inj. sc inclisiran and placebo control 300 mg (day-1, day-90 then every six months) • Placebo (174) and inclisiran (171)	• 345 Asian patients with ASCVD or high-risk of ASCVD	Mean percentage change from baseline LDL-C	Day 330	LDL-C reduction of 57.2% (p<0.001 *vs* placebo)	62

Up to now, real-world data (RWD) on short-term effectiveness remain limited. In a single-centre real-life population, inclisiran have been reported to be safely achieved LDL-C targets within one month, with significant reductions observed soon after the first dose.(74) A meta-analysis confirmed robust effectiveness and convenient dosing in real-world settings. However, the discrepancies with RCTs indicate a need for further RWD studies to address gaps in effectiveness and improve therapeutic outcomes.(75)

Future Directions for Indonesian Policy Regarding Use of PCSK9i and Inclisiran

Amid the persistent evidence gaps in dyslipidaemia management in Indonesia, the SMART-REACH model indicates that a substantial proportion of Indonesian patients with ASCVD face markedly elevated 10-year and lifetime risks of recurrent MACE.(76) These findings therefore strongly support the incorporation of these innovative

drugs into Indonesia's national dyslipidaemia and ASCVD guidelines. Furthermore, given the large affected population, rigorous post-marketing surveillance is essential to investigate adverse events.

Although inclisiran has been approved by the Indonesian regulatory agency since 2024, The Indonesia's Health Social Security Administering Body has not yet approved it for the universal health coverage (UHC) program. Therefore, cost-effectiveness analysis (CEA) or cost utility analysis (CUA) studies should be conducted to expedite the provision of this life-saving medications in UHC. In China, if inclisiran is priced at USD 2,973.5/per injection, then the combined use of this drug and statin is not cost-effective compared with statin alone.(77) However, for patients with familial hypercholesterolaemia or mixed dyslipidaemia at the chosen willingness-to-pay (WTP) threshold, inclisiran + standard of care (SoC), evolocumab + SoC and alirocumab + SoC are more cost effective in Singapore, compare to the use of SoC alone.(78)

CEA results for PCSK9i and inclisiran varied significantly across countries, primarily due to differences in drugs cost, WTP thresholds, and healthcare system. So, even though PCSK9i and inclisiran might be appropriate for some high-risk groups in certain upper-middle and high-income countries, their cost remains an obstacle in most developing countries. To increase access and guarantee equitable use, the government should implement strategy and policy like price negotiation, tiered pricing, pooled procurement, and context-specific WTP thresholds.(79)

Conclusion

For patients at high risk of ASCVD, silencing PCSK9 with siRNA is a simple, efficient, and well-tolerated method that significantly lowers LDL-C levels and may potentially improve ASCVD outcomes, but further studies are ongoing. Compared with other lipid-lowering therapies, such as PCSK9i, inclisiran's infrequent dosing, which is administered twice yearly, when given as monotherapy or in conjunction with statins, may further improve prognosis and clinical outcomes. Ongoing clinical trials are expected to broaden the therapeutic applications of inclisiran.

Authors Contribution

AWS and BD made substantial contributions to the work, including drafting and critically revising the manuscript, provided final approval of the published version, and agree to be accountable for all aspects of the work.

Ethical Statement

Ethical approval and informed consent were not required for this work.

Conflict of Interest

The authors have no conflict of interest in this paper. The figure(s) presented in this article were developed with the assistance of artificial intelligence (AI)-based tools to support visualization and graphical design. The authors reviewed, edited, and approved the final content to ensure accuracy and scientific integrity.

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