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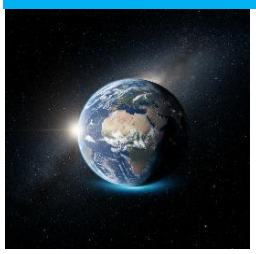

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PCSK9 inhibitors in the prevention of vascular events - a review of current evidence

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ABSTRACT

Background. Atherosclerotic cardiovascular disease remains the leading cause of mortality worldwide. Despite the widespread use of high-intensity statins, many patients fail to achieve target low-density lipoprotein cholesterol (LDL-C) levels and remain at high residual risk. Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors represent a novel class of lipid-lowering therapies that significantly reduce LDL-C and cardiovascular risk.

Aim. This review summarizes current evidence on the efficacy, safety, and clinical application of PCSK9 inhibitors, including monoclonal antibodies, small interfering RNA, and emerging oral agents, in preventing cardiovascular and cerebrovascular events.

Material and methods. A narrative review of literature from PubMed/MEDLINE, Embase, and Cochrane Library databases (January 2015–November 2025) was conducted. Search terms included "PCSK9 inhibitors," "evolocumab," "alirocumab," "inclisiran," "cardiovascular outcomes," and "MACE." Priority was given to randomized controlled trials, systematic reviews, and clinical guidelines.

Results. Monoclonal antibodies (evolocumab, alirocumab) reduce LDL-C by ~60% and major adverse cardiovascular events by 15–20% in secondary prevention. The VESALIUS-CV trial (2025) showed a 25% reduction in first cardiovascular events in high-risk primary prevention. Inclisiran enables sustained lipid reduction with twice-yearly dosing. Emerging oral agents (e.g., enlicitide) show comparable efficacy. Data from over 90,000 patients confirm a favorable safety profile without significant neurocognitive or diabetes-related risks.

Conclusions. PCSK9 inhibitors are effective and safe in reducing vascular events. Their role is expanding from secondary to primary prevention in high-risk or statin-intolerant patients. Future research should address long-term outcomes and novel approaches such as gene-editing therapies.

Key words: PCSK9 inhibitors, evolocumab, alirocumab, inclisiran, cardiovascular prevention, LDL-C.

Introduction

Atherosclerotic cardiovascular disease (ASCVD) persists as the primary driver of global morbidity and mortality, necessitating aggressive management of dyslipidemia, the central modifiable risk factor for vascular events.[1] The causal link between low-density lipoprotein cholesterol (LDL-C) and the progression of atherosclerosis is well-documented, with meta-analyses from the Cholesterol Treatment Trialists' (CTT) Collaboration demonstrating that every 1 mmol/L (approximately 38.7 mg/dL) reduction in LDL-C confers a 22% relative risk reduction in major vascular events.[2] While hydroxymethylglutaryl-CoA (HMG-CoA) reductase inhibitors, or statins, have been the cornerstone of lipid management for decades, a significant proportion of patients—up to two-thirds—remain unable to reach their individualized lipid goals through statin monotherapy alone.[3, 35] This "residual risk" is particularly prevalent in very-high-risk populations, such as those with familial hypercholesterolemia (FH) or recurrent acute coronary syndromes (ACS).[5]

The discovery of proprotein convertase subtilisin/kexin type 9 (PCSK9) in 2003 marked a turning point in lipidology.[7] PCSK9 is a serine protease, primarily synthesized in the liver, that regulates the density of LDL receptors (LDLR) on the surface of hepatocytes.[2] By binding to the LDLR, PCSK9 triggers its internalization and subsequent lysosomal degradation, preventing the receptor from recycling back to the cell surface to clear circulating LDL particles.[9] Genetic studies showing that individuals with loss-of-function variants in the PCSK9 gene possessed lifelong low LDL-C levels and a profound protection against cardiovascular disease provided the impetus for the development of therapeutic inhibitors.[2]

Since the regulatory approval of the first monoclonal antibodies (mAbs) in 2015, the pharmacological landscape of PCSK9 inhibition has expanded rapidly.[2] The field currently encompasses fully human monoclonal antibodies (evolocumab and alirocumab), small interfering RNA (siRNA) therapies (inclisiran), and emerging technologies such as oral small molecule macrocyclic peptides (enlicitide) and CRISPR-based gene editing (VERVE-101).[2] These agents have demonstrated the ability to lower LDL-C levels to unprecedented depths, supporting the "lower is better" paradigm of cardiovascular prevention.[14]

Clinical guidelines have evolved in tandem with these developments. The 2025 Focused Update of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) Guidelines for the Management of Dyslipidaemias has formalized aggressive targets, including LDL-C levels below 55 mg/dL for very-high-risk patients and below 40 mg/dL for those at "extreme risk".[16] As evidence for the benefits of intensive lipid-lowering continues to grow—extending into primary prevention and specialized vascular outcomes like stroke and peripheral artery disease (PAD)—the role of PCSK9 inhibitors is shifting from last-line therapy to an integral component of early, intensive combination regimens.[11] This review provides a comprehensive analysis of the current evidence regarding PCSK9 inhibitors in the prevention of vascular events, examining their biological mechanisms, landmark clinical outcomes, safety profiles, and the implementation barriers that limit their widespread adoption.

Research materials and methods

This scientific review utilizes a narrative synthesis approach to evaluate the current state of knowledge regarding PCSK9 inhibitors in cardiovascular prevention. The primary objective

was to consolidate evidence from landmark clinical trials and contemporary meta-analyses to provide a nuanced understanding of their role in clinical practice.

The literature search was conducted across three primary medical databases: PubMed/MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL). The search window focused on the decade between 2015 and 2025, corresponding to the period of significant clinical development and real-world deployment of PCSK9-targeted therapies. Key search terms included MeSH headings and free-text strings such as "proprotein convertase subtilisin/kexin type 9," "evolocumab," "alirocumab," "inclisiran," "MK-0616," "cardiovascular outcomes," "major adverse cardiovascular events," "MACE," "secondary prevention," and "statin intolerance."

The selection criteria for this review emphasized high-quality clinical data:

Phase 3 randomized, double-blind, placebo-controlled trials (RCTs) with clinical endpoints (e.g., FOURIER, ODYSSEY OUTCOMES, VESALIUS-CV, ORION program).

Systematic reviews and meta-analyses published in peer-reviewed journals that aggregated safety and efficacy data (e.g., stroke prevention, diabetes risk, neurocognitive outcomes).

Official guidelines and position papers from major international societies, including the 2024/2025 updates from the ESC, EAS, American Heart Association (AHA), and American College of Cardiology (ACC).

Early-phase results for novel delivery mechanisms (oral agents, base editing) presented at major cardiology conferences (AHA Scientific Sessions 2023-2025, ESC Congress 2024-2025).

A total of 17 RCTs involving 88,086 patients were identified for specific analyses of stroke prevention.[20] For comparative efficacy and safety, network meta-analyses incorporating data from over 64,000 subjects were utilized to contrast alirocumab and evolocumab.[21] Data extraction prioritized hazard ratios (HR), relative risks (RR), absolute risk reductions (ARR), and percentage changes in lipid parameters (LDL-C, ApoB, Lp(a)). Scientific notation and mathematical units were maintained as reported in the primary literature. The review synthesizes these facts into a cohesive narrative that explores the evolution of the field, from biological discovery to the current clinical standard of care.

Pathophysiology and the PCSK9 Pathway

The physiological regulation of LDL-C is largely dependent on the recycling of the low-density lipoprotein receptor (LDLR) on the surface of hepatocytes. The LDLR is a transmembrane protein that binds to apolipoprotein B-100 (ApoB-100) on the surface of LDL particles.[2] Once the LDL-LDLR complex is formed, it is internalized through clathrin-mediated endocytosis into an endosome. Within the endosome’s acidic environment, the LDLR undergoes a conformational change that releases the LDL particle, which is then sent to the lysosome for degradation. Under normal circumstances, the LDLR is subsequently recycled back to the plasma membrane, where a single receptor molecule can mediate the clearance of up to 100 LDL particles over its lifetime.[2, 58]

PCSK9, a 692-amino acid protein primarily synthesized in the liver, acts as a pivotal regulator of this process. It is secreted into the blood as a mature protein after autocatalytic cleavage. Once in the circulation, PCSK9 binds to the epidermal growth factor-like repeat A (EGF-A) domain of the LDLR on the hepatocyte surface.[2] This binding prevents the LDLR from assuming the recycled conformation after endocytosis. Instead, the PCSK9-LDLR complex is directed toward the lysosome, where both the protein and the receptor are degraded.[2] Consequently, higher levels of circulating PCSK9 lead to a reduction in the density of LDLRs on the cell surface, resulting in decreased clearance of LDL-C from the blood and elevated plasma levels of atherogenic lipoproteins.[9]

The therapeutic rationale for inhibiting PCSK9 is to prevent this receptor degradation, thereby increasing the number of active LDLRs available to remove cholesterol from the blood. This mechanism is distinct from and complementary to the mechanism of statins. While statins increase LDLR expression by inhibiting intracellular cholesterol synthesis, they also inadvertently increase the expression of PCSK9, which can blunt the overall lipid-lowering effect.[17] By combining a statin with a PCSK9 inhibitor, clinicians can achieve synergistic LDL-C reductions that are not possible with monotherapy.[3, 28, 39]

Table 1. Summary of the PCSK9 pathway and the impact of therapeutic inhibition.

Pathway Component	Physiological Role	Impact of High PCSK9	Impact of PCSK9 Inhibition
LDLR Density	Clears circulating LDL-C	Reduced (Degradation)	Increased (Recycling)
LDL-C Levels	Transport of lipids	Elevated (High risk)	Profoundly Reduced
Lp(a) Levels	Pro-thrombotic lipid	Baseline (Genetic)	Reduced by ~25%
ApoB Particles	Atherogenic marker	High particle count	Significantly lowered

Source: [2]

Furthermore, PCSK9 appears to exert effects beyond simple lipid transport. It is expressed in the vascular wall, including in endothelial cells, smooth muscle cells, and macrophages.[6] Research indicates that PCSK9 may promote the formation of foam cells by suppressing ABCA1-dependent cholesterol efflux and enhancing CD36-mediated lipid uptake.[26] It also influences vascular aging and senescence through the modulation of oxidative stress and inflammatory pathways.[8] These pleiotropic effects suggest that PCSK9 inhibitors may provide vascular protection through multiple mechanisms, including plaque stabilization and the suppression of pro-inflammatory cytokines like IL-6 and TNFα.[6]

Pharmacological Landscape: From Antibodies to Genetic Medicines

The therapeutic arsenal for targeting PCSK9 has expanded from the initial monoclonal antibodies to include a diverse array of modalities, each with unique pharmacokinetic profiles and administration schedules.

Monoclonal Antibodies (mAbs)

Evolocumab and alirocumab are the two primary monoclonal antibodies approved for clinical use. They are fully human IgG antibodies that bind with high affinity to circulating PCSK9 in the plasma.[6, 55] By neutralizing PCSK9 extracellularly, they prevent its interaction with the LDLR EGF-A domain.

Administration: These agents are administered via subcutaneous injection, typically using a pre-filled autoinjector pen.[6]

Dosing: Evolocumab is dosed at 140 mg every two weeks or 420 mg monthly. Alirocumab is typically initiated at 75 mg every two weeks, with the option to uptitrate to 150 mg every two weeks for patients requiring more intensive reduction.[6]

Efficacy: Both agents provide an average LDL-C reduction of 60%, which is sustained over

long-term follow-up.[21]

Small Interfering RNA (siRNA)

Inclisiran represents a novel approach that acts intracellularly to silence the synthesis of the PCSK9 protein. It consists of a chemically synthesized, double-stranded siRNA conjugated to GalNAc, which targets the molecule specifically to the liver via the asialoglycoprotein receptor.[2] Once inside the hepatocyte, the siRNA enters the RNA-induced silencing complex (RISC), where it facilitates the degradation of PCSK9 mRNA.[2, 43, 49]

Administration: Subcutaneous injection by a healthcare professional.[6]

Dosing: After an initial dose and a second dose at 90 days, maintenance therapy is required only once every six months.[2]

Efficacy: Inclisiran provides a sustained LDL-C reduction of approximately 50-52%, offering a convenient "vaccine-like" regimen for lipid management.[1]

Oral PCSK9 Inhibitors

A major development in the field is the advent of orally bioavailable inhibitors. Enlicitide decanoate (formerly MK-0616) is a macrocyclic peptide designed to bind to PCSK9 and inhibit its interaction with the LDLR with the same specificity as an antibody.[12]

Mechanism: It utilizes a small molecule approach to target the large protein-protein interface of PCSK9 and the LDLR.[33]

Efficacy: Phase 3 trials (CORALreef program) demonstrated LDL-C reductions of up to 55.8-60.9%, positioning it as a potent oral alternative to injectables.[12]

Permanent Gene Editing

Base-editing technologies like VERVE-101 and VERVE-102 are currently being investigated as "one-and-done" therapies. VERVE-101 uses CRISPR-based adenine base editing to introduce a precise single-nucleotide change (A-to-G) in the PCSK9 gene in the liver, permanently inactivating it.[13]

Mechanism: Lipid nanoparticles (LNPs) deliver the base editor mRNA and guide RNA to the liver via intravenous infusion.[13]

Efficacy: Early Phase 1 data (heart-1 trial) showed PCSK9 protein reductions of up to 84% and LDL-C reductions of 55%, with effects sustained for at least 18 months following a single infusion.[13]

Major Cardiovascular Outcomes Trials (Secondary Prevention)

The clinical validation of PCSK9 inhibitors was achieved through large-scale, event-driven cardiovascular outcomes trials (CVOTs). These studies proved that the massive LDL-C reductions achieved by these agents translate into meaningful clinical benefits.

The FOURIER Trial (Evolocumab)

The FOURIER (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk) trial was a randomized, double-blind study involving 27,564 patients with stable ASCVD (prior MI, prior stroke, or symptomatic PAD) who were already receiving moderate-to-high-intensity statins.[14]

Baseline Status: Median baseline LDL-C was 92 mg/dL.[14]

Results: Evolocumab reduced LDL-C by 59%, to a median of 30 mg/dL. At a median follow-up of 2.2 years, the primary composite endpoint (CV death, MI, stroke, hospitalization for

unstable angina, or coronary revascularization) occurred in 9.8% of the evolocumab group vs. 11.3% of the placebo group (HR 0.85; 95% CI 0.79–0.92; $p < 0.001$).[14]
Secondary Endpoint: The key secondary endpoint (CV death, MI, or stroke) was reduced by 20% (HR 0.80; 95% CI 0.73–0.88).[38]
Temporal Benefit: The risk reduction for the secondary endpoint improved from 16% in the first year to 25% beyond 12 months, illustrating a "legacy effect" or accrual of benefit over time.[14]

The ODYSSEY OUTCOMES Trial (Alirocumab)

The ODYSSEY OUTCOMES trial enrolled 18,924 patients who had experienced an ACS within the preceding 1–12 months and had elevated LDL-C ($\geq$ 70 mg/dL) despite maximally tolerated statins.[5]
Baseline Status: Median baseline LDL-C was 87 mg/dL.[29]
Results: Alirocumab reduced the primary MACE endpoint (coronary heart disease death, nonfatal MI, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization) by 15% (HR 0.85; 95% CI 0.78–0.93; $p < 0.001$).[29]
Mortality: Notably, alirocumab was associated with a 15% reduction in all-cause mortality (3.5% vs. 4.1%; HR 0.85; p=0.026).[29] While the hierarchical testing did not permit definitive statistical significance for CV death, the numerical trend was strong, particularly in patients with baseline LDL-C $\geq$ 100 mg/dL.[29]
Subgroup Analysis: Patients with baseline LDL-C $\geq$ 100 mg/dL experienced a 24% reduction in MACE (ARR 3.4%) and a 28% reduction in all-cause death.[29]

Table 2: Relative risk reductions for major vascular endpoints in landmark CVOTs.[31]

Endpoint	FOURIER (Evolocumab) HR	ODYSSEY OUTCOMES (Alirocumab) HR
Primary MACE	0.85 (0.79–0.92)	0.85 (0.78–0.93)
Myocardial Infarction	0.73 (0.65–0.82)	0.86 (0.77–0.96)
Ischemic Stroke	0.79 (0.66–0.95)	0.73 (0.57–0.93)
All-Cause Mortality	1.05 (0.88–1.25)	0.85 (0.73–0.98)

Source: [31,38]

Primary Prevention: The VESALIUS-CV Breakthrough

For years, the use of PCSK9 inhibitors was clinically restricted to secondary prevention. However, the VESALIUS-CV (TIMI 66) trial, reported in November 2025, provided landmark evidence for their use in high-risk primary prevention.[11]
The trial investigated 12,257 adults with no history of a heart attack or stroke but who had either established atherosclerosis (without a major event) or high-risk diabetes.[11] Participants were randomized to subcutaneous evolocumab (140 mg every 2 weeks) or placebo on top of high-intensity statins for a median follow-up of 4.6 years.[11]
Primary Outcome: Evolocumab significantly reduced the risk of coronary heart disease death, heart attack, or ischemic stroke by 25% (HR 0.75; 95% CI 0.64–0.88; $p < 0.001$).[11]
First Heart Attack: There was a 36% reduction in the risk of a first myocardial infarction ($p < 0.001$).[11]

Extended Composite: A 19% reduction was observed in a broader endpoint including ischemia-driven arterial revascularization.[11]
LDL-C Control: At 48 weeks, evolocumab lowered LDL-C by 55%, from a median of 115 mg/dL to 45 mg/dL.[11]
The VESALIUS-CV results are clinically transformative, representing the first demonstration that any non-statin agent can significantly improve cardiovascular outcomes in a primary prevention population already treated with high-intensity lipid-lowering therapy.[11] It underscores the importance of intensive LDL-C lowering to achieve targets around 40 mg/dL to prevent the first major cardiovascular event.[11]

Evidence for RNA-Interfering Therapy (Inclisiran)

Inclisiran differs from monoclonal antibodies in its biological durability. The ORION clinical trial program has provided robust evidence for its lipid-lowering efficacy.
ORION-9 (Heterozygous FH): Achieved a placebo-corrected LDL-C reduction of 47.9% at 18 months.[2]
ORION-10 and ORION-11 (ASCVD/Risk Equivalent): Demonstrated sustained reductions of approximately 50-52% over 18 months, even on a background of maximally tolerated statins.[2]
ORION-18 (Asian Population): Reported a 57.2% reduction in LDL-C at day 330, with more than 70% of participants achieving ≥ 50% reduction.[2]
Long-term Stability: The ORION-8 trial, with over 12,000 patient-years of exposure, confirmed that inclisiran provides consistent LDL-C lowering for up to 6.8 years without attenuation of effect or new safety signals.[42]
While the event-driven ORION-4 trial is still ongoing to definitively prove MACE reduction, a pooled meta-analysis of Phase 3 trials showed a promising trend, with a 20% numerical reduction in major cardiovascular events (RR 0.80; 95% CI 0.64–1.02; p=0.07).[1] Real-world data from the VICTORION-Difference trial (2025) recently showed that inclisiran brought significantly more high-risk patients to their guideline-recommended LDL-C goals at 90 days compared to standard care (84.9% vs. 31.0%; OR 12.09).[44]

Specialized Vascular Outcomes: Stroke and Peripheral Artery Disease

Stroke and Cerebrovascular Prevention

A comprehensive meta-analysis of 17 RCTs (88,086 patients) focused specifically on stroke prevention.[20]
Risk Reduction: PCSK9 inhibitors reduced the incidence of any stroke from 1.2% in control groups to 0.8% in intervention groups (RR 0.76; 95% CI 0.66–0.86; p < 0.001).[20]
Hemorrhagic Stroke: Crucially, there was no increase in the risk of intracranial hemorrhage (RR 0.86; p=0.68), a safety concern often cited with extremely low cholesterol levels.[15]
Acute Ischemic Stroke: Post hoc analysis of patients with acute non-cardiogenic ischemic stroke found that adding evolocumab to atorvastatin within 24 hours of onset significantly reduced the incidence of Early Neurological Deterioration (END) in the large artery atherosclerosis (LAA) subtype (14.0% vs. 28.0%; p=0.006).[27] This combination was also associated with a higher proportion of favorable functional outcomes (mRS 0-2) at 90 days.[27]

Peripheral Artery Disease (PAD) and Limb Events

Patients with PAD represent a subgroup with extremely high vascular risk.
MACE in PAD: In the FOURIER trial, patients with PAD experienced a significant reduction

in MACE (9.5% vs. 13.0%; p=0.004). Because their absolute event rates were higher than those without PAD, the absolute risk reduction was significantly greater.[37]
Major Adverse Limb Events (MALE): PCSK9 inhibition resulted in a 42% relative risk reduction in major adverse limb events (0.27% vs. 0.45%; p=0.0093). This includes reductions in acute limb ischemia, major amputation, and urgent revascularization.[37]
Lp(a) Interaction: In ODYSSEY OUTCOMES, the reduction in major PAD events was particularly pronounced in patients with high baseline levels of lipoprotein(a), an independent genetic risk factor for PAD that is effectively lowered by PCSK9 inhibitors by about 25%.[29]

Safety, Tolerability, and the "Very Low LDL-C" Question

The safety of achieving very low LDL-C levels (e.g., < 25 mg/dL or < 15 mg/dL) has been a central topic of clinical debate. Systematic reviews of over 90,000 patients have provided reassuring data.[15]

Neurocognitive Function

The EBBINGHAUS study used the Cambridge Neuropsychological Test Automated Battery (CANTAB) to evaluate cognitive function in patients reaching extremely low LDL-C levels on evolocumab.[46]
Findings: No significant difference in executive function, memory, or reaction time was observed between patients on evolocumab vs. placebo.[46]
Long-term Data: Follow-up for over 8 years in the FOURIER-OLE study demonstrated no increase in neurocognitive adverse events, dementia, or Alzheimer's disease.[30] Mendelian randomization studies also show that individuals with lifelong low LDL-C due to PCSK9 variants do not have an increased dementia risk.[46]

Diabetes Mellitus

Meta-analyses have assessed whether PCSK9 inhibition, like statin therapy, increases the risk of new-onset diabetes.
Results: There is no significant increase in the relative risk of developing diabetes mellitus (RR 1.05; 95% CI 0.95–1.17; p=0.32).[10]
Specific Inhibitors: In some analyses, alirocumab was actually associated with a significant *reduction* in diabetes-related adverse events compared to control groups (RR 0.91; p=0.02).[10]

General Safety and Local Reactions

PCSK9 inhibitors are generally well-tolerated.
Discontinuation: Rates of study drug discontinuation due to adverse events are similar to placebo (~3-4%).[33]
Local Reactions: Injection-site reactions (redness, itching, swelling) are the most common adverse effect, occurring in approximately 3-7% of patients vs. 2-5% for placebo.[10]
Liver and Muscle: Incidences of liver enzyme elevation (ALT > 3x ULN) and muscle-related concerns (CK > 10x ULN) are identical to placebo.[29]

Evolving Clinical Guidelines: 2024 and 2025 Updates

Reflecting the strength of the clinical evidence, international guidelines have become increasingly aggressive regarding lipid targets and the use of PCSK9 inhibitors.

2025 ESC/EAS Focused Update

The European Society of Cardiology and European Atherosclerosis Society published a 2025 Focused Update to the 2019 Dyslipidemia Guidelines.[16]

Extreme Risk Category: A new category for patients with recurrent ASCVD events within two years while on optimal treatment, recommending an LDL-C target of < 40 mg/dL.[16]

Very High Risk: Target LDL−C < 55 mg/dL and ≥ 50% reduction from baseline.[18]

High Risk: Target LDL-C < 70 mg/dL.[51]

Early Initiation: The guidelines strongly emphasize initiating intensive lipid-lowering therapy, including PCSK9 inhibitors, during the index hospitalization for ACS to ensure rapid goal achievement.[19]

2025 ACC/AHA ACS Guidelines

The 2025 ACC/AHA Guideline for the Management of Patients with Acute Coronary Syndromes similarly reinforces early combination therapy.[53]

Class I Recommendation: Adding a nonstatin agent (ezetimibe or PCSK9 inhibitor) is recommended for patients on maximally tolerated statins with LDL-C ≥ 70 mg/dL.[53]

Intensification: It is considered reasonable (Class IIa) to further intensify therapy if LDL-C is between 55 and 70 mg/dL in this high-risk population.[53]

Economic Considerations and Global Implementation

The primary hurdle to the widespread use of PCSK9 inhibitors is economic rather than clinical.

Cost-Effectiveness and ICERs

The cost-effectiveness of these agents varies significantly by region and patient risk profile.

United States: At an initial list price of $14,000 annually, the ICER was estimated at $337,729/QALY. Manufacturers reduced list prices by 60% in 2018 to approximately $5,850, which improved accessibility but still left ICERs above some willingness-to-pay thresholds.[54]

Developing Countries: In China, ICERs can reach $281,762/QALY, making them unaffordable for the general population. However, in Mexico and Saudi Arabia, evolocumab has been found cost-effective in high-risk post-MI patients with ICERs below $50,000/QALY.[56]

Real-World Spanish Study: A prospective analysis found an ICER of EUR 51,427/QALY, supporting their economic rationale when used in appropriately targeted high-risk populations.[59]

Barriers to Adoption

Despite the clinical benefits, less than 1% of patients with established ASCVD are taking these medications.[12]

Therapeutic Inertia: Nearly 40% of cardiologists have never prescribed a PCSK9 inhibitor, often relying on statins alone despite failing to reach targets.[12]

Logistical Barriers: Requirements for prior authorization, specialized storage (refrigeration for mAbs), and patient education on injections contribute to low utilization.[12]

Access Abandonment: High out-of-pocket costs result in nearly 33% of patients abandoning their prescriptions at the pharmacy.[54]

Discussion

The clinical trajectory of PCSK9 inhibitors from a novel mechanism to a primary driver of vascular event prevention represents a paradigm shift in cardiovascular medicine. The evidence accumulated over the last decade, culminating in the late-breaking 2025 trials, supports several critical insights into modern lipid management and vascular health.

The Erosion of the Threshold Concept

Historically, many clinicians adhered to a threshold concept where reaching an LDL-C level of 70 mg/dL was considered "enough." The FOURIER and ODYSSEY OUTCOMES trials, and most recently the VESALIUS-CV trial, have effectively dismantled this view.[11] The data consistently show a linear, monotonic relationship between LDL-C reduction and vascular event reduction, with no evidence of a floor effect down to levels as low as 15 mg/dL.[37] This has empowered the 2025 guidelines to push targets into the 40 mg/dL and 55 mg/dL ranges, recognizing that for every millimole of additional reduction, patients gain another 22% reduction in relative risk.[2]

Timing and Plaque Stability: The "Strike Early" Approach

One of the most profound insights from recent research is the importance of timing. The ODYSSEY OUTCOMES trial showed that starting PCSK9 inhibition soon after an ACS event provides immediate benefit.[29] The newer SHAWN and PCSK9-PROVE trials are investigating initiation *during* or immediately after percutaneous coronary intervention (PCI) for acute stroke or MI.[6] The rationale is that early, intensive lipid-lowering does more than just lower LDL-C; it modifies plaque phenotype and inhibits the acute inflammatory surge (IL-6) associated with vascular events.[6] This "strike early, strike strong" approach is now a Class I recommendation in the latest guidelines, shifting the paradigm from gradual titration to upfront intensive combination therapy.[19]

The Adherence Paradox: siRNA and Oral Agents

The major real-world limitation of monoclonal antibodies has been adherence. Despite their efficacy, bi-weekly injections are a barrier for many. The introduction of inclisiran addresses this through a biannual dosing schedule.[2] Interestingly, real-world data suggest that while inclisiran provides slightly less potent LDL-C reduction than mAbs (50% vs. 60%), its adherence-adjusted impact on MACE may be superior because a much higher proportion of patients remain on therapy (79% high-adherence for inclisiran vs. 56% for mAbs).[6]

The oral inhibitor enlicitide (MK-0616) represents the next frontier. By delivering antibody-level efficacy in a pill, it removes the "needle barrier" and may be more easily integrated into primary care practices.[12] If the CORALreef Outcomes trial confirms hard cardiovascular benefit, oral PCSK9 inhibitors could potentially replace injectables for a vast majority of the population.

Permanent Solutions and Ethical Considerations

The emergence of base editing (VERVE-101) as a "one-and-done" treatment raises fascinating clinical and ethical questions.[13] The prospect of permanently lowering a patient's LDL-C through a single infusion could virtually eliminate the issue of non-adherence and therapeutic inertia. However, the permanency of gene editing means that any unanticipated long-term side effects cannot be reversed by simply stopping a drug. While early safety data

are promising in high-risk populations, the threshold for moving such technology into lower-risk primary prevention will be significantly higher than for reversible therapies like oral pills or bi-annual injections.[13]

Addressing the Implementation Gap

The most significant contradiction in the field remains the discrepancy between the "excellent results" in clinical trials and the "low utilization" in routine practice.[1] The "high cost" and "therapeutic inertia" identified across global studies suggest that medical progress has outpaced the financial and logistical capacity of healthcare systems.[56] Solving this implementation gap will require more than just new molecules; it necessitates a multifaceted approach involving price reductions, simplified prior authorization processes, and a shift in physician mindset toward early combination therapy rather than the traditional stepwise titration of statins.[12]

Conclusions

The collective evidence from 2015 to 2025 establishes proprotein convertase subtilisin/kexin type 9 inhibitors as a cornerstone of modern vascular prevention. These agents provide a potent, safe, and reliable mechanism to reduce low-density lipoprotein cholesterol by 50-60%, translating into a 15-20% reduction in major adverse cardiovascular events in secondary prevention. The landmark VESALIUS-CV trial has now extended this evidence into primary prevention, demonstrating a 25% reduction in major vascular events for high-risk individuals who have not yet suffered a heart attack or stroke.

Furthermore, PCSK9 inhibitors have shown specialized efficacy in reducing ischemic stroke risk and preventing major adverse limb events in patients with peripheral artery disease. Their safety profile is robust; long-term studies of over 90,000 patients have definitively addressed concerns regarding neurocognitive function and diabetes risk, showing that extremely low levels of cholesterol are well-tolerated and clinically beneficial.

As the field moves forward, the focus will shift toward optimizing delivery through long-acting interfering RNA and oral macrocyclic peptides, while permanent gene-editing solutions remain on the horizon. The 2025 guideline updates reflect this progress by moving targets to unprecedented depths and advocating for early combination therapy. The ultimate goal of contemporary lipid management—moving from reactive treatment to proactive prevention—is now biologically and clinically achievable through the intelligent application of proprotein convertase subtilisin/kexin type 9 inhibition.

Disclosure

Author's Contribution

Conceptualization: Michał Rucki
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