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EDITING OUT CARDIOVASCULAR RISK: A NARRATIVE REVIEW OF GENE-EDITING APPROACHES TO PCSK9

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ABSTRACT

Background: PCSK9 is a circulating protease that regulates plasma low-density lipoprotein (LDL) cholesterol levels. It binds to the LDL receptor on the surface of hepatocytes and directs the receptor toward intracellular degradation, so that greater PCSK9 activity leaves fewer LDL receptors available to clear LDL-C from the bloodstream. PCSK9 was established as a drug target largely through human genetics: naturally occurring loss-of-function variants are associated with lifelong low LDL-C and a markedly reduced risk of atherosclerotic cardiovascular disease with no apparent adverse consequences, whereas gain-of-function variants cause a severe, early onset form of familial hypercholesterolemia. Pharmacological PCSK9 inhibitors, monoclonal antibodies, and small interfering RNA (siRNAs) are currently in clinical use; however, all require repeated, lifelong administration.

Aim: This review argues that PCSK9 gene editing has progressed from a theoretical concept to an emerging therapeutic class, with three distinct technical strategies currently under active development. We compared CRISPR-Cas9 nuclease knockout, base editing, and epigenetic silencing with established antibody and siRNA classes, focusing on efficacy, durability, and safety.

Materials and Methods: A search of relevant research databases and a hand search of selected journals were conducted to identify eligible papers.

Results: Several programs based in the United States and China have demonstrated that a single dose of a gene-editing agent can lower PCSK9 and LDL-C levels in humans and animal models. Nuclease-mediated knockout and base editing produced the largest reductions, whereas epigenetic silencing produced a smaller but reversible effect. The principal safety signal identified to date was attributed to the lipid-nanoparticle delivery vehicle, rather than the editing mechanism itself.

Conclusions: Early clinical and preclinical evidence supports the feasibility of PCSK9 gene editing. The remaining gaps are long-term safety data, direct evidence of reduced cardiovascular events rather than biomarker changes alone, and a strategy for equitable access and pricing.

KEYWORDS

PCSK9, CRISPR Base Editing, Gene Editing, Epigenetic Silencing, LDL Cholesterol, Cardiovascular Disease

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1. Introduction

Low-density lipoprotein cholesterol (LDL-C) is a well-established causal risk factor for atherosclerotic cardiovascular disease (ASCVD). PCSK9 regulates circulating cholesterol levels by modulating the number of LDL receptors (LDLR) on the hepatic cell surface. It binds to the receptor and directs it toward intracellular degradation, which lowers the hepatic clearance of plasma LDL-C. Human population genetics studies have shown that individuals carrying naturally occurring loss-of-function variants in PCSK9 have lifelong low LDL-C levels and a markedly reduced risk of coronary disease, with no apparent adverse effects, whereas gain-of-function variants cause a severe, early onset form of familial hypercholesterolemia (FH). This “natural evidence” gave scientists strong prior confidence that pharmacologically lowering PCSK9 activity in adults would be both effective and well-tolerated.

Two classes of PCSK9-lowering therapies are currently in clinical use. Monoclonal antibodies: Evolocumab and alirocumab bind directly to circulating PCSK9 proteins, and large outcome trials (FOURIER for evolocumab and ODYSSEY OUTCOMES for alirocumab) have demonstrated reduced rates of major adverse cardiovascular events on top of statin therapy. Their principal limitation is the dosing burden: both require subcutaneous injection every two–four weeks, indefinitely. Inclisiran, a small interfering RNA (siRNA) therapeutic, directly reduces hepatic PCSK9 synthesis and requires dosing only twice yearly.

Gene editing offers a conceptually different approach: rather than repeatedly inhibiting the PCSK9 protein or its messenger RNA, an editing agent alters the gene itself or its regulatory state in a single administration, with the goal of durable or permanent reduction in PCSK9 production. Three distinct editing mechanisms have been

tested in animal models and, in several cases, in humans: (1) CRISPR-Cas9 nuclease-mediated knockout, which introduces a double-strand break to disrupt the gene; (2) base editing, which converts a single DNA base without cutting both strands; and (3) epigenetic silencing, which uses a catalytically inactive CRISPR protein to repress transcription without altering the underlying DNA sequence.

2. Methodology

2.1 Review Design

This is a narrative rather than a systematic review. A narrative approach was chosen because the evidence base for PCSK9 gene editing remains small and heterogeneous, spanning mechanistic and animal studies to early phase human trials. Some of the most recent results are available only through clinical trial registries or company disclosures rather than peer-reviewed publications, under which a systematic review would not be appropriate.

2.2 Information Sources

The research was conducted using the PubMed and Google Scholar databases, clinical-trial registries (principally ClinicalTrials.gov and the Chinese Clinical Trial Registry), and specialist gene-editing news sources (CRISPR Medicine News, Innovative Genomics Institute, BioSpace, and TCTMD).

2.3 Limitations of This Methodology

This review has two major limitations: First, as a narrative rather than a systematic review, study selection remains more susceptible to bias than a fully systematic process. Second, this is an unusually fast-moving field; several results summarized here were disclosed within the 12 months preceding this review and may already be superseded by newer data, particularly for VERVE-102, ART002, YOLT-101, and STX-1150.

3. Results

3.1 Baseline Comparator: Pharmacological PCSK9 Inhibition

Monoclonal antibodies remain the most clinically mature class of PCSK9 inhibitors. In the FOURIER outcomes trial, which included 27,564 patients with established ASCVD followed for a median of 2.2 years, evolocumab reduced LDL-C to a median of 30 mg/dL, and the magnitude of benefit on a key secondary endpoint grew from 16% in the first year of treatment to 25% thereafter, consistent with a delayed, cumulative cardiovascular benefit rather than an immediate one.

Alirocumab produced a comparable reduction in LDL-C in the ODYSSEY OUTCOMES trial, which enrolled 18,924 patients within twelve months of an acute coronary syndrome. Across the full trial population, all-cause death was 15% lower with alirocumab than with placebo (hazard ratio 0.85); the benefit was concentrated among patients with higher baseline LDL-C levels. Both antibodies require subcutaneous injection every two–four weeks, indefinitely.

Inclisiran, a small interfering RNA (siRNA) therapeutic, silences hepatic PCSK9 messenger RNA, preventing protein synthesis rather than neutralizing the protein after secretion. In the pivotal ORION-10 and ORION-11 trials, inclisiran reduced LDL-C by 52.3% and 49.9%, respectively, relative to placebo, with a safety profile similar to that of placebo, except for a higher rate of mild injection-site reactions. Dosing is required only twice yearly after an initial course, which is a markedly lighter burden than the antibody class; however, inclisiran remains a chronic repeat-administration therapy.

3.2 Permanent Disruption: CRISPR-Cas9 Knockout

AccurEdit Therapeutics, based in China, was among the first to report human dosing data for an in vivo CRISPR-Cas9 nuclease knockout of the PCSK9 gene. Its candidate, ART002, delivers Cas9 messenger RNA and a single guide RNA within a lipid nanoparticle to hepatocytes, where it is designed to permanently disrupt the PCSK9 gene. In an investigator-initiated trial that began in mid-2024, the company reported in February 2025 that the medium- and high-dose cohorts achieved average PCSK9 protein reductions of approximately 90% (maximum 93%), which was described by the company as exceeding the reduction reported for inclisiran, together with LDL-C reductions of up to 70% after a single intravenous dose. AccurEdit's disclosures describe a favorable safety profile to date, although independent, peer-reviewed confirmation of these figures was not located for this review and should be obtained before the data inform any clinical decisions.

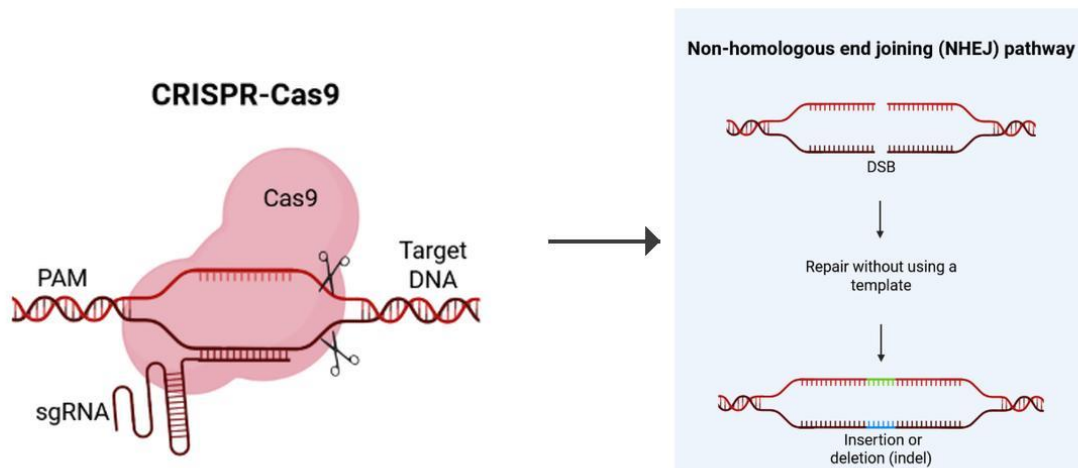


Fig. 1. Illustration of CRISPR-Cas9 knockout mechanism, Cas9 enzyme creates a double-strand break (DSB), the cell attempts to fix the break using an error-prone pathway called Non-Homologous End Joining, that frequently introduces random insertions or deletions (indels) at the cut site, These indels cause frameshift mutations, leading to premature stop codons and a completely non-functional protein. Modified from reference [16] (Xu, J. (2025) <https://BioRender.com/m6qkiei>

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3.3 Single-Letter Correction: Base Editing

Verve Therapeutics' VERVE-101 was among the first in vivo base-editing therapies to be tested in humans for any indication. It delivers an adenine base editor, as messenger RNA, together with a guide RNA in a lipid nanoparticle, converting a single DNA base at a splice donor site in PCSK9 without cutting both DNA strands. In non-human primates, this approach reduced blood PCSK9 protein by 83% and LDL-C by 69%, with effects lasting for at least 476 days after a single dose. A related preclinical study reported a similar outcome: approximately 90% PCSK9 reduction and 60% LDL-C reduction, which was stable for at least eight months.

In the first-in-human Heart-1 trial, 13 patients were dosed across four dose levels before enrollment was paused. Among the first five patients in the 0.45 mg/kg cohort with at least 28 days of follow-up, time-averaged LDL-C reductions ranged from 21% to 73% (averaging 46%), and in the two patients followed for the longest duration, the reduction remained durable for nine months. On April 2, 2024, however, Verve paused enrollment after the sixth patient dosed at 0.45 mg/kg experienced a serious, drug-related adverse event within four days: a Grade 3, asymptomatic elevation in liver enzymes (ALT) together with Grade 3 thrombocytopenia, both of which resolved fully within days without bleeding or other symptoms. The company attributed the laboratory abnormalities to the lipid-nanoparticle delivery vehicle rather than to the editing mechanism and reported the event to regulators in the United States, United Kingdom, and New Zealand.

Verve's redesigned successor, VERVE-102, retains the same base editor and guide RNA but uses a different ionizable lipid and GalNAc-targeted nanoparticle intended to improve tolerability. Preliminary data from the first two dose cohorts, reported in late 2024, showed no serious adverse events or laboratory abnormalities. Full results from the Heart-2 Phase 1b trial, published in the New England Journal of Medicine in May 2026, reported that a single dose of VERVE-102 produced dose-dependent, substantial, and sustained reductions in PCSK9 and LDL-C. Eli Lilly acquired Verve Therapeutics in June 2025 to continue the development of this and related programs; no further results have been disclosed.

Another example of a base editor currently undergoing trials is YOLT-101, developed by YolTech Therapeutics, which is currently in a Phase 1 investigator-initiated trial in China and has received clearance to begin IND-enabling studies in China and the US for heterozygous familial hypercholesterolemia (HeFH).

In the six patients treated with the highest dose (0.6 mg/kg), interim data at four months showed an average 50% drop in LDL cholesterol and over 70% reduction in PCSK9 protein levels. No serious adverse events were observed.

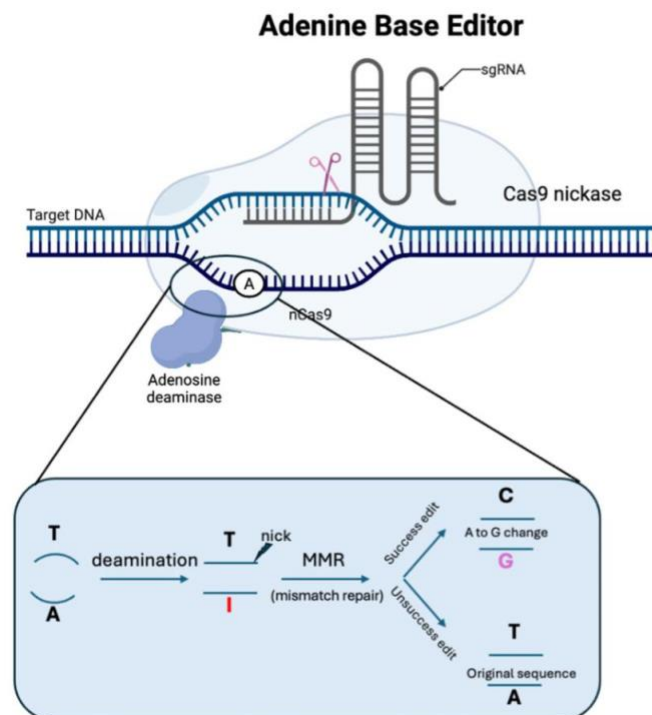


Fig. 2. Illustration of Adenine base editor. After introducing single stranded break adenine base editor exploit the mismatch repair (MMR) mechanism to achieve the desired base editing outcome. [16] . Created in BioRender, Xu, J. (2025) <https://BioRender.com/pkbwuq4>

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3.4 Reversible Regulation: Epigenetic Silencing

The most mechanistically distinct approach comes from Scribe Therapeutics, whose lead candidate, STX-1150, uses a platform the company terms ELXR (Epigenetic Long-Term X-Repressor): a catalytically inactive, CasX-derived CRISPR protein fused to epigenetic effector domains that deposit repressive histone and DNA-methylation marks at the PCSK9 locus. Because the underlying DNA sequence is never cut or rewritten, this approach is explicitly designed to be durable yet reversible, in contrast to permanent base editing or knockout. In non-human primate studies reported in 2026, a single dose of an STX-1150 prototype reduced LDL-C by up to 68%, and the lowest tested dose sustained LDL-C reductions greater than 50% for more than 22 months of ongoing follow-up, and circulating PCSK9 fell by approximately 90% in the same animals.

Scribe Therapeutics obtained regulatory clearance from Australia's Therapeutic Goods Administration to begin a first-in-human, open-label, single-ascending-dose study of STX-1150, with enrollment underway in Australia as of mid-2026 and additional sites planned in New Zealand. If successful, STX-1150 would be the first PCSK9 therapy to achieve gene silencing without cutting or rewriting DNA sequences.

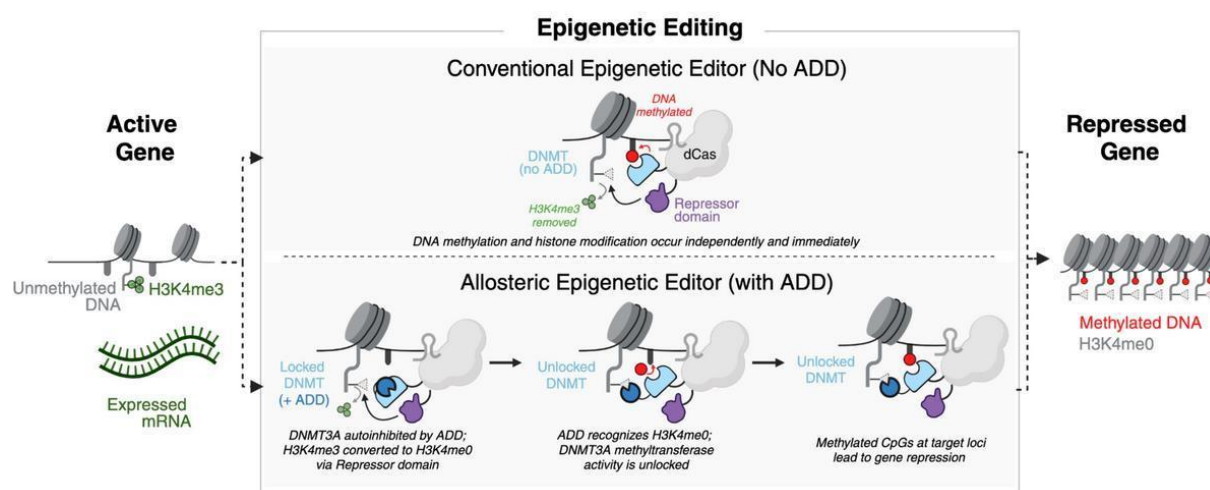


Fig. 3. Stepwise mechanism of allosteric epigenetic silencing. Adopted from Charles et al. (2026) BioRxiv,

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3.5 Safety Signals Across Editing Platforms

In recent years, the safety of human genome manipulation has become a key research topic. Large, unintended DNA deletions are a well-documented consequence of double-strand break repair. Unlike Cas9 nuclease, base editors and prime editors are designed to avoid creating breaks in the first place, since they nick rather than cut, and a 2025 Nature Communications analysis confirmed the difference in practice: such deletions occur roughly 20-fold less often with base and prime editors than with conventional Cas9 nuclease cutting — supporting the argument for favoring non-cutting or single-base-change approaches where feasible.

Unfortunately, nuclease-based editing carries risks that current prediction tools do not fully detect. A 2023 whole-genome analysis found large chromosomal deletions at off-target sites that went undetected by standard guide RNA similarity screening.

Within the PCSK9 programs reviewed here, the one serious safety signal reported to date — the ALT elevation and platelet drop in Heart-1 — was attributed by the sponsor to the lipid-nanoparticle delivery vehicle, not to off-target editing, and VERVE-102's redesigned delivery system has so far avoided similar events. The broader pattern points in the same direction: delivery-vehicle risk and editing-fidelity risk appear largely separable and merit evaluation as distinct safety questions, rather than being lumped together as "gene-editing risk."

3.6 Comparative Summary

Table 1 summarizes the modalities, lead programs, and reported outcomes discussed above. The figures for AccurEdit, Scribe, and CTX310 are drawn substantially from company disclosures and trade-press reporting rather than from peer-reviewed publication; these should be treated as preliminary

Table 1. Comparative summary of PCSK9-lowering methods, by mechanism.

Modality	Lead Program	PCSK9 ↓	LDL-C ↓	Key Safety Signal	Stage (mid-2026)
Monoclonal antibody	Evolocumab (FOURIER)	n/a	~60%	Well tolerated	Approved
Monoclonal antibody	Alirocumab (ODYSSEY OUTCOMES)	n/a	~60%	Well tolerated	Approved
siRNA	Inclisiran (ORION-10/-11)	Substantial	~50–52% at day 510	Well tolerated; safety profile similar to placebo	Approved
CRISPR base editing	Verve VERVE-101 (Heart-1)	Dose-dependent	Up to 73% at 0.45 mg/kg	Enrollment paused after Grade 3 ALT rise + Grade 3 thrombocytopenia in one patient	Paused; informed VERVE-102 redesign
CRISPR base editing	Verve/Lilly VERVE-102 (Heart-2)	Dose-dependent	Dose-dependent, substantial, sustained	No treatment-related serious adverse events reported in initial cohorts	Phase 1b, published NEJM May 2026
CRISPR-Cas9 knockout	AccurEdit - ART002	~90%, max 93%	Up to ~70%	Company-reported favorable safety profile; not yet independently confirmed	Phase 1 (China), ongoing
Epigenetic silencing	Scribe STX-1150 (ELXR)	Up to ~90% (NHP)	Up to 68% (NHP); >50% sustained ≥22 mo at lowest dose	No DNA sequence change; designed to be reversible	First-in-human dosing underway (Australia/NZ, mid-2026)

Note. Figures for AccurEdit ART002, Scribe STX-1150 are drawn from company and trade-press disclosures rather than peer-reviewed publications and should be treated as preliminary. NHP = non-human primate

4. Discussion

4.1 The Durability–Reversibility Spectrum

The three editing mechanisms reviewed here occupy different positions on a durability–reversibility spectrum. Nuclease knockout and base editing both alter the DNA sequence permanently: once a hepatocyte is edited, it and its progeny cannot revert to producing PCSK9 at pretreatment levels. Epigenetic silencing, in contrast, is explicitly designed to be durable without being permanent; Scribe frames reversibility as a deliberate design choice rather than a limitation. Which property is preferable is not self-evident and likely depends on context. A permanent edit may be appropriate for a young patient with severe familial hypercholesterolemia who would otherwise face decades of injections, whereas reversibility may be preferable as a precautionary feature for a broader, lower-risk population receiving a preventive, one-time treatment for the first time. Human follow-up is not yet long enough to establish whether a reversible edit actually attenuates over years in patients as it appears to in non-human primates, or whether a permanent edit carries any unanticipated long-term liability that a reversible approach would avoid. The irreversibility of genomic therapy is a double-edged sword for the patient: while it precludes the possibility of withdrawing from treatment, it also ensures that the individual cannot be stripped of the treatment's benefits against their will.

4.2 Separating Delivery-Vehicle Risk from Editing-Fidelity Risk

A recurring theme across the sources reviewed is that the most serious safety signal observed to date in human PCSK9-editing trials (the Heart-1) ALT and platelet abnormality was attributed to the lipid-nanoparticle carrier rather than to the base-editing mechanism, and Verve's redesign for VERVE-102 altered the delivery-vehicle chemistry while leaving the editor and guide RNA unchanged. This distinction is clinically meaningful: a program's overall risk profile depends jointly on the fidelity of the editing enzyme itself. Evaluating a reported adverse event therefore requires identifying which of these two risk axes it implicates.

4.4 Regulatory and Funding Landscape

A true single-dose therapy cannot easily be discontinued if a late safety signal emerges, which is part of the rationale for the extended participant follow-up built into these programs. In parallel, the pace of any individual program depends substantially on the surrounding research-funding environment. A 2026 update from the Innovative Genomics Institute reported that, in 2025, more than 7,500 NIH or NSF grants were suspended or cancelled amid broad cuts to U.S. federal research funding; courts have since reinstated some of these, though the report could not yet quantify how many CRISPR-related trials had, in turn, been delayed. This is potentially significant in comparative terms: AccurEdit, based in China, reached human PCSK9-editing dosing on a broadly similar timeline to Verve's U.S.-based programs, and any sustained slowdown in U.S.-funded research could widen rather than narrow that gap.

4.5 Equity and Access

Currently available chronic PCSK9 inhibitors illustrate a well-documented access problem: despite proven efficacy, real-world adherence to indefinite injectable regimens is consistently low. A one-time genomic therapy could, in principle, eliminate the adherence problem, since there is no regimen to discontinue once the dose is administered. It would likely, however, substitute a different access barrier: a single infusion priced to recoup the cost of developing a genomic medicine is plausibly a substantial up-front expense, in contrast to a chronic drug whose cost is typically insured and distributed across many years. None of the sources reviewed addressed pricing directly, since none of the PCSK9-editing programs have yet reached a regulatory submission, let alone a list price; this is accordingly identified as an open question for future work rather than a finding of this review.

5. Conclusions

Liver-targeted gene editing has moved from theoretical concept to emerging therapeutic class in under four years. Independent programs demonstrated that nuclease knockout, base editing, and epigenetic silencing holds promise as single-dose treatment for dyslipidemia, a condition that has traditionally required lifelong management.

Long-term safety and cardiovascular outcomes data remain absent, delivery-vehicle tolerability continues to be refined, and no programme reviewed here has seriously addressed how a one-time genomic intervention would be priced or accessed at scale.

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Conflicts of Interest: The authors declare no conflicts of interest.

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