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THE ROLE OF PCSK9 INHIBITORS IN HYPERLIPIDEMIA AND CARDIOVASCULAR DISEASES

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Abstract

Background: Elevated low-density lipoprotein cholesterol (LDL-C) is a causal risk factor for atherosclerotic cardiovascular disease (ASCVD). Objective: To summarize the mechanisms, efficacy, cardiovascular outcomes, safety, and clinical positioning of monoclonal antibody PCSK9 inhibitors, with attention to hepatic impairment. Methods: A narrative review of the clinical trials FOURIER and ODYSSEY OUTCOMES, the 2019 ESC/EAS dyslipidaemia guideline and its 2025 focused update, and product labeling. Results: In FOURIER, evolocumab reduced LDL-C by 59% relative to placebo at 48 weeks and reduced the primary composite cardiovascular endpoint (9.8% vs 11.3%; hazard ratio 0.85). In ODYSSEY OUTCOMES, alirocumab reduced the primary endpoint after acute coronary syndrome (9.5% vs 11.1%; hazard ratio 0.85). Conclusions: PCSK9 monoclonal antibodies provide substantial additional LDL-C lowering and reduce cardiovascular events in selected high-risk populations. Evidence does not establish a special clinical advantage in advanced liver disease; treatment must follow individual assessment and product labeling [1–4, 6].

Keywords: PCSK9 inhibitors; hyperlipidemia; LDL cholesterol; atherosclerosis; evolocumab; alirocumab; cardiovascular outcomes.

Introduction

LDL-C contributes causally to the development of ASCVD. Lowering LDL-C is therefore central to prevention in patients at elevated cardiovascular risk [5]. Statins remain first-line pharmacotherapy, frequently combined with ezetimibe when additional LDL-C reduction is needed. Even with maximally tolerated therapy, some patients remain above their risk-based LDL-C goal or cannot tolerate an effective statin regimen [3, 4].

Proprotein convertase subtilisin/kexin type 9 (PCSK9) promotes degradation of the hepatic LDL receptor. Inhibiting circulating PCSK9 preserves receptor recycling and increases clearance of LDL particles. Evolocumab and alirocumab are injectable monoclonal antibodies against PCSK9 [1, 2]. This review examines their mechanistic and clinical evidence and addresses the narrower question of whether their pharmacology justifies preferential use in patients with hepatic dysfunction.

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The liver removes most circulating LDL particles by means of LDL receptors on the surface of hepatocytes. After an LDL particle enters the cell, its receptor can return to the cell surface and bind another particle. PCSK9 changes this cycle: when it attaches to the receptor, the receptor is more likely to be broken down instead of reused. Fewer available receptors mean slower removal of LDL-C from the bloodstream. This simple receptor pathway helps explain why blocking PCSK9 can lower LDL-C even when a patient is already taking a statin [5, 6].

The therapeutic question is practical. People with established coronary, cerebral, or peripheral atherosclerotic disease may continue to have high LDL-C after treatment with statins. Others have inherited high LDL-C levels or find that they cannot continue a recommended statin dose. In these situations, a drug acting through a different step in the LDL-receptor cycle can be considered. The purpose of this paper is to explain what the outcome trials actually show, where clinical guidelines place PCSK9 antibodies, and what remains unknown in people with liver disease [1–4].

It is useful to separate a change in a laboratory value from a change in health outcomes. A lower LDL-C value is an important biological response, but patients and clinicians also need to know whether treatment reduces heart attack, stroke, or other cardiovascular events. Large randomized trials address this second question by comparing patients assigned to active treatment with those assigned to placebo while other recommended care continues. Their findings apply most directly to people similar to those enrolled in the trials [1, 2].

Materials and Methods

This is a narrative, non-systematic literature review; no original patient cohort, pooled estimate, or newly collected outcomes are reported. The evidence base comprises the original randomized cardiovascular outcomes reports of FOURIER and ODYSSEY OUTCOMES [1, 2], European dyslipidaemia guidance and its focused update [3, 4], a consensus statement on LDL causality [5], and the prescribing information for evolocumab [6]. Data were extracted descriptively for study population, LDL-C change, primary cardiovascular endpoint, adverse effects, clinical indications, and hepatic-impairment limitations. Because the sources and populations differ, no cross-trial indirect efficacy comparison or formal meta-analysis was attempted.

The two main outcome studies were chosen because they report both lipid measurements and patient-centered cardiovascular endpoints. FOURIER examined evolocumab in people with established ASCVD, while ODYSSEY OUTCOMES examined alirocumab after a recent acute coronary syndrome [1, 2]. The guidelines were used to describe clinical placement rather than treated as original trial data [3, 4]. Product labeling was used for dose schedules and the limits of information on hepatic impairment [6].

The review does not present a claim that every published PCSK9 study was captured. There was no prespecified database search, inclusion flow diagram, independent screening, or assessment of publication bias. Accordingly, the descriptions below should be read as an explanatory synthesis of selected high-quality sources rather than as estimates from a

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systematic review. Numerical event rates are reported with their own trial populations and follow-up periods to avoid misleading comparisons.

For clarity, LDL-C refers to low-density lipoprotein cholesterol; ASCVD refers to atherosclerotic cardiovascular disease; and a hazard ratio below 1 indicates fewer observed primary events in the active-treatment arm during trial follow-up. An absolute difference in event rates tells a different story from a relative reduction. Reporting both helps readers understand the scale of benefit without assuming that all patients will experience the same effect [1, 2].

The focus on monoclonal antibodies is deliberate. PCSK9 can be targeted by other technologies, but their dosing, clinical programs, and evidence should be reviewed separately rather than merged with those of evolocumab and alirocumab. The term "PCSK9 inhibitors" in the title therefore refers chiefly to the antibodies examined in the cited cardiovascular outcome trials. This distinction makes the numerical findings easier to interpret and prevents a result observed with one specific product from being automatically assigned to every medicine affecting the same protein [1, 2, 6].

The interpretation of study endpoints followed three rules. First, an LDL-C percentage change is described as a lipid outcome rather than proof that an individual will avoid a future event. Second, the composite primary endpoint is reported as a whole without implying that every component changed by the same amount. Third, a finding in patients already receiving intensive background treatment is discussed as evidence for adding treatment in a comparable setting. These rules are simple, but they avoid common errors when clinical trial results are retold in a review article [1, 2].

Results

Mechanism and lipid response. PCSK9 binding favors lysosomal degradation of the LDL receptor; monoclonal antibodies interrupt this extracellular interaction. In FOURIER, 27,564 patients with established ASCVD and LDL-C of at least 70 mg/dL (or non-HDL-C at least 100 mg/dL) receiving statin therapy were randomized to evolocumab or placebo. The relative LDL-C reduction was 59% at 48 weeks; median LDL-C fell from 92 to 30 mg/dL in the evolocumab group [1].

Cardiovascular outcomes. Over a median 2.2 years in FOURIER, the primary composite endpoint occurred in 9.8% with evolocumab and 11.3% with placebo (hazard ratio 0.85; 95% confidence interval 0.79–0.92). In ODYSSEY OUTCOMES, 18,924 patients with a recent acute coronary syndrome and persistent atherogenic lipoprotein elevation despite intensive or maximally tolerated statins were randomized to alirocumab or placebo. Over a median 2.8 years, the primary composite endpoint occurred in 9.5% versus 11.1% (hazard ratio 0.85; 95% confidence interval 0.78–0.93) [1, 2]. These are outcomes from different randomized comparisons against placebo, not a direct comparison of the two antibodies.

Administration and tolerability. Evolocumab is administered subcutaneously at 140 mg every 2 weeks or 420 mg monthly according to its prescribing information [6]. Both

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outcomes trials identified injection-site reactions as a relevant tolerability consideration; long-term safety and adherence require follow-up in routine care [1, 2].

Why monoclonal antibodies work. Evolocumab and alirocumab bind circulating PCSK9, leaving more LDL receptors available for repeated use by the liver. They act outside the cell and are given by injection. Statins, by comparison, reduce the body's production of cholesterol and increase LDL-receptor expression through a different mechanism. Combining approaches can therefore lead to further LDL-C reduction when the first treatment alone is insufficient. The antibody does not remove plaque directly; improved lipid levels may help slow the process that creates plaque over time [1, 5, 6].

Understanding the FOURIER population matters. Its participants already had clinical ASCVD and were receiving background statin therapy. The study therefore tested additional treatment in patients with persistent risk, not whether an antibody should replace statins in all people with raised cholesterol. The trial's primary endpoint combined several cardiovascular outcomes. A reduction from 11.3% to 9.8% is an absolute difference of 1.5 percentage points over the observed median follow-up; the hazard ratio of 0.85 describes relative event occurrence during follow-up. These two measures are compatible, but they answer different questions [1].

ODYSSEY OUTCOMES addressed another clinically important group: patients who had recently experienced acute coronary syndrome and still had elevated atherogenic lipoprotein levels despite intensive or maximally tolerated statin treatment. In that setting, the primary endpoint fell from 11.1% in the placebo group to 9.5% in the alirocumab group, an absolute difference of 1.6 percentage points over the study period. The study supports added treatment in selected patients after an acute event. It does not prove the same absolute effect in people who have never had ASCVD or in patients with very different baseline risks [2].

LDL-C change and event reduction should not be presented as identical outcomes. A large LDL-C reduction is measurable relatively soon after treatment begins, whereas the prevention of a cardiovascular event may take longer to observe. Trial results summarize many patients, and an individual's expected benefit depends on their baseline risk, previous events, initial LDL-C, other illnesses, and length of treatment. For that reason, the decision to intensify therapy is based on both the lipid measurement and the broader clinical picture [1–4].

Inherited lipid disorders form another reason to consider intensified LDL-C lowering. In familial hypercholesterolemia, LDL-C may remain high from a young age because of impaired clearance of LDL particles. An intervention that preserves functioning LDL receptors can help when there is sufficient residual receptor activity. The exact treatment decision still depends on the person's phenotype, risk category, previous treatment response, and applicable guidance. This article does not infer a separate clinical outcome estimate for familial hypercholesterolemia from the two outcome trials [3, 4, 6].

Safety should be described in proportion to the evidence. Local reactions where an injection is given can occur. Any suspected adverse reaction should be assessed in the context of the patient's other medicines and medical conditions. The large trials provide

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valuable comparative safety information during their follow-up, but no trial can establish that an uncommon or very late event is impossible. A treatment plan should therefore include follow-up of LDL-C response, tolerability, and the patient's ability to continue the prescribed schedule [1, 2, 6].

The LDL receptor is recycled many times under normal conditions. PCSK9 does not create cholesterol; its importance lies in reducing the number of receptors that can clear LDL from blood. When an antibody binds PCSK9, more receptors can return to the cell surface. The resulting change in circulating LDL-C follows a plausible biological pathway, but this mechanism alone could not have established cardiovascular benefit. The value of the outcome trials is that they tested whether the biological effect was accompanied by fewer clinical events in randomized patient groups [1, 2, 5].

The word "risk" can refer to an individual's chance of an event or to the relative difference between groups. For example, the 15% relative reduction described by a hazard ratio of 0.85 should not be read as meaning that 15 out of every 100 treated people necessarily avoid an event. The actual proportion of patients with a primary event differed by about one to two percentage points between arms during the respective trial follow-up periods. A person at much lower underlying risk could have a smaller absolute benefit even if a similar relative effect applied; a person at higher risk could have a larger one. Such extrapolations remain estimates rather than direct trial observations [1, 2].

It also matters what counted as an event. The primary outcomes were composites: each study combined several clinically meaningful cardiovascular events into one prespecified measure. A composite can provide enough events to assess treatment reliably, yet it must be read carefully because the components differ in severity and frequency. Readers should consult the original trials for each component and should avoid summarizing the composite as simply "cardiovascular death prevented." The trials support fewer combined cardiovascular events, while any claim about one particular outcome should cite its own corresponding analysis [1, 2].

Discussion

The cardiovascular results support PCSK9 monoclonal antibodies as add-on options for appropriately selected patients with residual LDL-C elevation despite maximally tolerated lipid-lowering therapy. ESC/EAS guidance positions them within a risk-based strategy that generally includes statins and ezetimibe; the 2025 focused update adds newer evidence without replacing the need to assess baseline risk and LDL-C response [3, 4]. For true statin intolerance, the tolerated background regimen and therapeutic options must be evaluated individually.

PCSK9 monoclonal antibodies are proteins degraded through catabolic pathways rather than conventional cytochrome P450 metabolism. This pharmacological distinction alone does not establish superior clinical outcomes or safety in hepatic disease. Evolocumab labeling reports no dose adjustment for mild to moderate hepatic impairment but states that data are unavailable for severe hepatic impairment [6]. Thus, the original manuscript's suggestion of particular benefit in early cirrhosis is not supported by the cited

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trials. FOURIER and ODYSSEY OUTCOMES primarily address cardiovascular risk in selected trial populations, not outcomes specific to cirrhosis [1, 2, 6].

This review is limited by its narrative selection of sources, lack of a reproducible systematic search, and absence of quantitative synthesis. Trial follow-up and eligibility criteria constrain extrapolation to patients with severe hepatic disease and to long-term use. Medication cost and access can also affect implementation. These limitations should be considered before generalizing the observed relative risk reductions to an individual patient.

A stepwise treatment approach starts by establishing cardiovascular risk and checking that the person is receiving a suitable dose of established lipid-lowering therapy. Clinicians then compare the measured LDL-C with the goal appropriate for that risk category, review adherence and tolerability, and consider adding another drug when needed. European guidance commonly places a PCSK9 antibody after a maximally tolerated statin and ezetimibe in patients at very high risk who remain above goal. The precise sequence can vary with clinical circumstances, and the 2025 update should be read together with the full guideline [3, 4].

Statin intolerance needs careful wording. A patient may have a symptom while taking a statin without the medicine being the sole cause. The severity of the symptom, previous doses, timing, and response to changes in treatment should be evaluated before deciding that all statins are unsuitable. If the patient truly cannot tolerate effective statin therapy, other LDL-C lowering treatments, including a PCSK9 antibody in an appropriate risk setting, may be considered. The evidence from trials conducted mainly on background statins should not be described as direct proof of identical outcomes for every statin-free regimen [1–4].

The issue of liver disease requires special care. Many circulating medicines undergo enzymatic metabolism in the liver, but a monoclonal antibody is broken down as a protein. That difference may reduce some types of metabolic drug interaction. It does not mean that all patients with liver disease have been studied, that liver function never matters, or that treatment is automatically preferable to a statin. For evolocumab, the prescribing information distinguishes mild or moderate hepatic impairment from severe hepatic impairment, for which data are unavailable. Liver disease can also change a patient's overall health priorities and the likely benefit of long-term prevention [6].

It is especially important not to equate fatty liver with cirrhosis. These conditions differ in severity and clinical implications. The trials summarized here were designed to test cardiovascular outcomes in their enrolled populations, not to compare people across stages of chronic liver disease. A claim that PCSK9 inhibitors improve liver function, prevent progression of cirrhosis, or are safer than every other lipid-lowering drug in advanced disease would require studies designed to answer those questions. The available evidence in this article cannot support such conclusions [1, 2, 6].

Treatment adherence is another part of effectiveness outside a trial. A less frequent injection schedule may be convenient for some patients, while others may prefer tablets or have difficulty arranging injections and follow-up. Affordability and access also vary by health system. These considerations affect whether the reduction in LDL-C seen under

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study conditions can be sustained in practice. A realistic treatment plan should therefore address access, instruction for correct administration, and reassessment of the LDL-C level after therapy is changed [3, 4, 6].

This paper has several limits. It draws mainly on two large trials and selected guideline and labeling documents; it is not a complete review of every available drug, dose, or patient group. The composite primary endpoints in the two trials include different event definitions and come from different populations. Their percentages cannot be pooled by simple addition or used to rank evolocumab against alirocumab. Follow-up was also limited relative to the many years over which atherosclerosis develops. Future work should examine long-term outcomes, access to treatment, and patients who were underrepresented in pivotal trials [1, 2].

One common clinical scenario is a person with an earlier myocardial infarction whose LDL-C remains above the recommended threshold after a tolerated high-intensity statin and ezetimibe. The relevant question is not only whether an antibody can lower LDL-C, but whether the expected additional reduction and the person's cardiovascular risk justify injections, cost, and follow-up. The trials support a discussion of additional therapy for patients resembling those studied. A different scenario is an otherwise healthy person with only a modest LDL-C rise; the same trial event rates should not be copied into that person's counseling [1–4].

Another scenario is a person with both ASCVD and chronic liver disease. The clinician first has to identify the nature and severity of liver disease, current medicines, the patient's life expectancy and priorities, and whether standard lipid-lowering treatment is truly contraindicated or merely presumed unsuitable. If a PCSK9 antibody is considered, the published product information and the evidence gap in severe hepatic impairment must be discussed. A low likelihood of cytochrome P450 interactions is a pharmacological observation, not a substitute for clinical data in decompensated cirrhosis [6].

Clear follow-up prevents an effective treatment from being judged too early or continued without knowing whether it is helping. A baseline lipid measurement establishes the starting point. A later measurement shows the achieved LDL-C response, while questions about injections, missed doses, reactions, and access help explain an unexpectedly small change. Management can then be adjusted according to risk, treatment goals, and the patient's circumstances. Neither a favorable laboratory number nor an injection schedule alone captures the whole clinical decision [3, 4, 6].

For a patient who reports muscle symptoms during statin treatment, the first discussion should establish what was taken, at what dose, when symptoms started, and whether the symptoms changed when therapy changed. Some patients can continue a lower or different statin regimen, while others need alternative treatment. This matters because "statin intolerant" is not one uniform research population. Decisions about adding a PCSK9 antibody should remain linked to cardiovascular risk and achieved LDL-C rather than to a vague label alone. This review does not provide a diagnostic algorithm for muscle symptoms; it explains why accurate characterization of previous treatment is necessary before interpreting the trial evidence [1–4].

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Finally, study findings should be communicated in language that patients can use. A clinician can explain that the injection helps the liver keep more of the receptors that remove LDL particles, that cholesterol levels can fall substantially, and that large trials found fewer combined cardiovascular events in specific high-risk groups. It is equally fair to explain that no medicine eliminates risk, that injections and monitoring remain necessary, and that evidence is limited in severe liver disease. Presenting both benefit and uncertainty makes the decision more accurate than promising an individual patient the average effect of a randomized trial [1, 2, 6].

The main research gap identified here is not whether PCSK9 antibodies lower LDL-C in the populations studied; that effect is well demonstrated. The harder questions concern people with markedly different baseline risk, advanced hepatic disease, long periods of treatment, and barriers to obtaining medication. Dedicated studies or carefully designed registries could clarify these issues. Until such evidence is available, clinicians should keep the established trial results and the unanswered questions separate. This distinction is particularly important in review writing, where a plausible mechanism can otherwise be mistaken for proof of a specific benefit in an unstudied group [1–4, 6].

One strength of the two pivotal trials is that their outcomes concern events patients recognize as serious, rather than cholesterol values alone. At the same time, a trial average is not a personalized prescription. A patient with several previous events and persistently raised LDL-C may have more to gain in absolute terms than one with a low short-term event risk. The same distinction matters when discussing treatment cost: the clinical value of an added medicine depends partly on who receives it. The cited guidelines address these decisions by using overall risk and response to previous therapy, rather than an isolated LDL-C number interpreted without context [1–4].

The interpretation of treatment response should also be consistent over time. LDL-C measured before intensification, a clearly documented background regimen, and a repeat value after a reasonable period make it possible to understand whether the additional medicine achieved the intended lipid effect. A poor response invites a review of missed injections, storage or administration problems, and changes in other medicines before concluding that the mechanism has failed. These are practical considerations, not new findings from the trials, and they do not replace attention to symptoms or adverse effects. In a review article, separating such clinical reasoning from demonstrated trial results helps readers understand the strength of each statement [1–4, 6].

Conclusion

Evolocumab and alirocumab substantially lower LDL-C and reduce composite cardiovascular events in the high-risk populations studied. Their use should be guided by cardiovascular risk, residual LDL-C, maximally tolerated background therapy, and individual safety considerations. Severe hepatic impairment remains an evidence gap, so a general claim of special benefit in cirrhosis is unwarranted [1–4, 6].

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References

1. Sabatine M. S., Giugliano R. P., Keech A. C. et al. Evolocumab and clinical outcomes in patients with cardiovascular disease // The New England Journal of Medicine. — 2017. — Vol. 376, no. 18. — P. 1713–1722. — DOI: 10.1056/NEJMoa1615664.
2. Schwartz G. G., Steg P. G., Szarek M. et al. Alirocumab and cardiovascular outcomes after acute coronary syndrome // The New England Journal of Medicine. — 2018. — Vol. 379, no. 22. — P. 2097–2107. — DOI: 10.1056/NEJMoa1801174.
3. Mach F., Baigent C., Catapano A. L. et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk // European Heart Journal. — 2020. — Vol. 41, no. 1. — P. 111–188. — DOI: 10.1093/eurheartj/ehz455.
4. Mach F., Koskinas K. C., Roeters van Lennep J. E. et al. 2025 Focused Update of the 2019 ESC/EAS Guidelines for the management of dyslipidaemias // European Heart Journal. — 2025. — Vol. 46, no. 42. — P. 4359–4378. — DOI: 10.1093/eurheartj/ehaf190.
5. Ference B. A., Ginsberg H. N., Graham I. et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies // European Heart Journal. — 2017. — Vol. 38, no. 32. — P. 2459–2472. — DOI: 10.1093/eurheartj/ehx144.
6. REPATHA (evolocumab): prescribing information [Electronic resource] / U.S. Food and Drug Administration. — 2026. — URL: https://www.accessdata.fda.gov/drugsatfda_docs/label/2026/125522s049lbl.pdf (accessed: 12.09.2026).