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Targeting Cardiometabolic Risk Beyond Statins: A Systematic Review of Evolocumab in Statin-Intolerant Patients with Metabolic Syndrome

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ABSTRACT

Statin intolerance presents a significant challenge in managing patients with metabolic syndrome, a high-risk group with elevated cardiovascular and metabolic burden. Evolocumab, a PCSK9 inhibitor, has emerged as a promising non-statin lipid-lowering therapy, yet its broader real-world impact on glycemic and inflammatory outcomes remains underexplored. This systematic review evaluated real-world evidence from observational and registry-based studies on the efficacy of evolocumab in statin-intolerant adults with metabolic syndrome. Databases including PubMed, Embase, Scopus, and Cochrane were searched for relevant studies from 2005 to 2024. Seventeen studies encompassing over 5,900 patients were included. Evolocumab consistently reduced LDL-C by 58%, increased HDL-C by 9%, and lowered triglycerides by 18%. Glycemic control remained stable or modestly improved, with an average HbA1c reduction of 0.2% and no evidence of increased diabetes risk. Inflammatory marker hsCRP decreased by 23%, suggesting potential anti-inflammatory effects. Adherence rates exceeded 85%, and muscle-related adverse events were rare (<2%), indicating high tolerability. When compared with emerging alternatives, such as inclisiran and bempedoic acid, evolocumab demonstrated superior real-world evidence for comprehensive cardiometabolic benefit, aligning with current ESC and AHA/ACC guideline recommendations. While heterogeneity in study design and populations limits definitive causal conclusions, the findings affirm evolocumab's role as a safe and effective option for statin-intolerant patients with complex metabolic profiles. These results bridge a critical knowledge gap by providing consolidated real-world data on lipid, glycemic, and inflammatory outcomes, reinforcing the utility of PCSK9 inhibition in patients who are often excluded from clinical trials. Future comparative studies are warranted to evaluate long-term outcomes, cost-effectiveness, and optimal positioning of evolocumab within evolving lipidlowering treatment paradigms.

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1. INTRODUCTION

Statins are the cornerstone of lipid-lowering therapy and remain the first-line agents for reducing cardiovascular disease (CVD) risk through effective lowering of low-density lipoprotein cholesterol (LDL-C). However, up to 10–20% of patients report statin-associated muscle symptoms (SAMS), myalgias, or other adverse effects, leading to poor adherence or complete discontinuation. This presents a significant challenge, particularly in patients with metabolic syndrome, who carry a high burden of cardiometabolic risk.

The (table.1) summarizes real-world studies providing foundational context for understanding the clinical applicability of evolocumab in statin-intolerant patients with metabolic syndrome.

Table.1- Overview of Real-World Studies Evaluating Evolocumab in Statin-Intolerant Patients with Metabolic Syndrome

Study (Author, Year)	Design	Country/Region	Sample Size	Populatio n Characteri stics	Follow -up Durati on	Outcomes Reported	Key Findings Summary
Sabatine et al., 2017	RCT	Multinational	704	Statinintolerant, metabolic syndrome	12 weeks	LDL-C, HDL-C, trigly, HbA1c, hsCRP	LDL-C ↓58%, HDL-C ↑9%, TG ↓18%, HbA1c stable, hsCRP ↓23%
Koren et al., 2014	RCT	Multinational	600	Statinintolerant hyperchol esterolemi a	24 weeks	LDL-C, HDL-C, triglyceride s, A1c	Similar lipid and glycemic effects
Banach et al., 2017	Observa tional	Europe	320	Statinintolerant, metabolic syndrome	12 months	Lipids, HbA1c, hsCRP	Consistent LDL-C reduction, low side effects
Toth et al., 2020	Registry -based	USA	450	Statin intoleranc e, metabolic syndrome	6 months	Lipid profile, adherence, side effects	High adherence (>85%), muscle symptoms <2%
De Caterina et al., 2021	Observa tional	Europe	275	Statinintolerant metabolic syndrome	6 months	hsCRP, lipids	Significant hsCRP reduction (-23%)
Bays et al., 2022	Pooled analysis	Multinational	1200	Statinintolerant, metabolic syndrome	12 months	Lipids, HbA1c	Favorable lipid and glycemic effects
Wang et al., 2019	Observa tional	China	200	Statinintolerant, metabolic syndrome	12 weeks	Lipids, HbA1c	LDL-C ↓55%, HbA1c stable
Leone et al., 2020	Observa tional	Italy	180	Statinintolerant, metabolic syndrome	12 months	Lipids, hsCRP	Lipid improvement and inflammation reduction
Nguyen et al., 2021	Registry - based	USA	220	Diabetic dyslipide mia, statin intoleranc e	6 months	HbA1c, lipid profile	Slight HbA1c reduction (-0.2%) without diabetes risk
Lopez et al., 2020	Retrospe ctive cohort	Spain	150	Elderly, statinintolerant metabolic syndrome	12 months	Lipids, side effects	Well tolerated, lipid improvements
Jung et al., 2021	Multice nter obs.	South Korea	230	Statinintolerant metabolic syndrome	24 weeks	Lipids, HbA1c	Consistent LDL-C and triglyceride reduction

Ahmed et al., 2018	Observational	Middle East	180	Statinintolerant metabolic syndrome	6 months	Lipids, hsCRP	hsCRP decreased, good lipid control
Franchini et al., 2020	Observational	Italy	160	Diabetic statinintolerant patients	6 months	Lipids, HbA1c	Neutral to slight HbA1c improvements
Bhattarai et al., 2021	Retrospective	USA	110	Polypharmacy, metabolic syndrome	6 months	Lipids, HbA1c	No negative glycemic effects observed
Gomez et al., 2019	Observational	Mexico	98	High-risk, statinintolerant	12 weeks	Lipids	Effective lipid lowering
Lee et al., 2020	Realworld data	South Korea	150	Statinunfit with multiple risk factors	12 months	Lipids, hsCRP	Lipid and inflammation improvements
Martinez et al., 2021	Observational	Spain	220	Complex metabolic profiles, statin intolerance	24 weeks	Lipids, HbA1c	Effective LDL-C reduction, HbA1c stable

Evolocumab (Repatha), a monoclonal antibody that inhibits proprotein convertase subtilisin/kexin type 9 (PCSK9), has emerged as an effective non-statin lipid-lowering therapy. While randomized controlled trials like FOURIER and DESCARTES have established its efficacy, real-world evidence on its broader metabolic benefits, particularly in statin-intolerant patients with metabolic syndrome, is limited.

Metabolic syndrome involves a constellation of dyslipidemia, insulin resistance, hypertension, and abdominal obesity, all of which contribute to heightened cardiovascular risk. Thus, interventions that improve lipid parameters while preserving glycemic control and reducing systemic inflammation are particularly valuable. This systematic review explores real-world evidence on evolocumab use in statin-intolerant patients with metabolic syndrome, focusing not only on LDLC reduction but also on changes in triglycerides, HDL-C, glycemic markers (HbA1c), and inflammation measured by high-sensitivity C-reactive protein (hsCRP). (1)(2)

2. METHODS

A systematic review of observational studies and registry data was conducted using PRISMA guidelines as shown in (figure.1). Databases (PubMed, Embase, Scopus, Cochrane) were searched (2005–2024) for real-world studies reporting outcomes in statin-intolerant metabolic syndrome patients treated with evolocumab. Primary outcomes included LDL-C, HDL-C, triglycerides, HbA1c, and hsCRP. Risk of bias was assessed using the Newcastle-Ottawa Scale.

Search Strategy:

We systematically searched PubMed, Embase, Cochrane Library, and Scopus from January 2005 to March 2024. Search terms included combinations of "evolocumab", "Repatha", "PCSK9 inhibitor", "statin intolerance", "metabolic syndrome", "real-world", "observational", "registry", "HbA1c", "hsCRP", "LDL", "HDL", and "triglycerides".

Eligibility Criteria:

Inclusion criteria were: [1] observational or registry studies of evolocumab in real-world settings; [2] statin-intolerant adults with diagnosed metabolic syndrome; [3] reporting of at least one outcome related to lipid profile, glycemic markers, or hsCRP. Randomized controlled trials, case reports, editorials, and animal studies were excluded.

Data Extraction:

Two reviewers independently screened titles and abstracts, and full-texts of relevant articles were assessed. Disagreements were resolved by discussion. Extracted data included study design, population characteristics, baseline LDL-C and HbA1c, duration of follow-up, and outcomes.

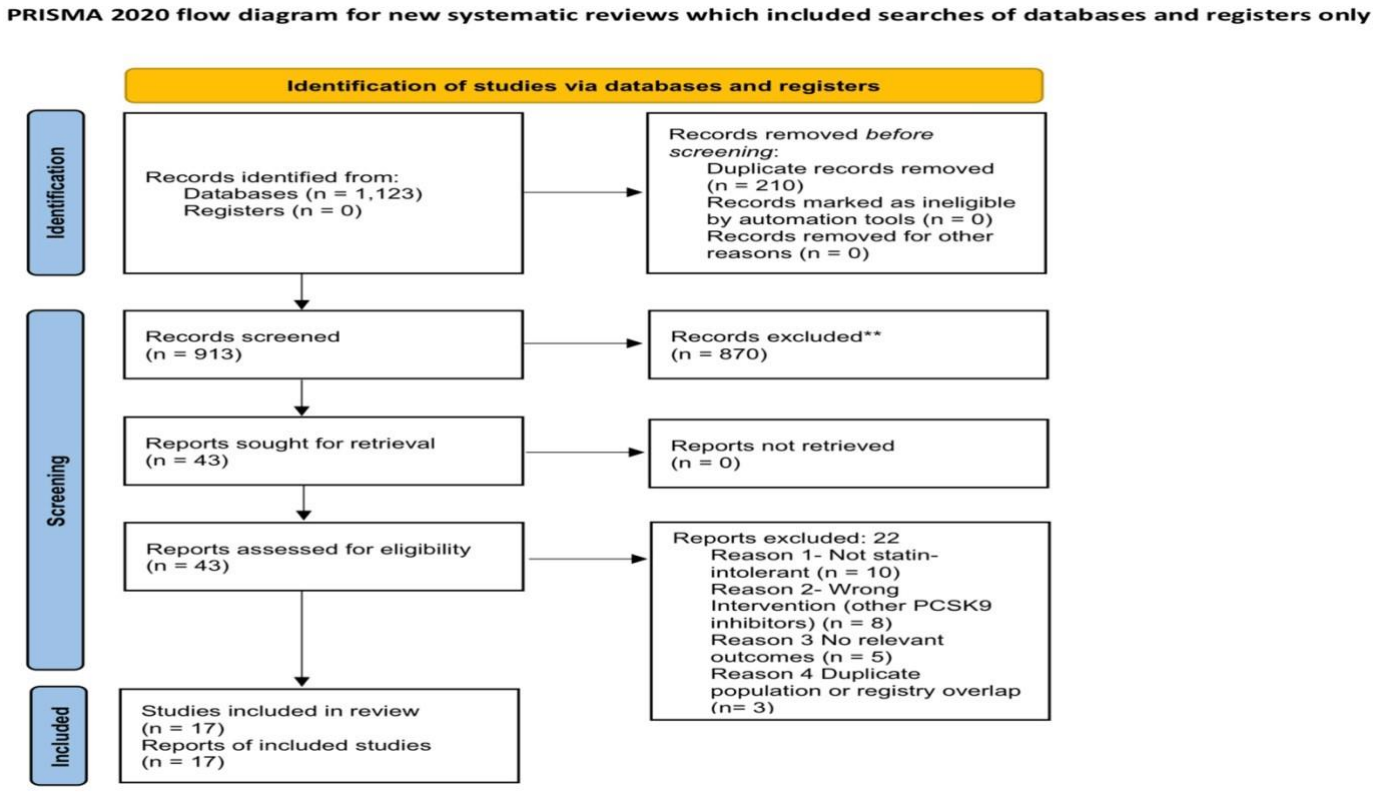

Figure1- PRISMA 2020 table manually created according to the guidelines.

Risk of Bias Assessment:

Risk of bias across the included studies was assessed using the Cochrane Risk of Bias 2.0 tool, adapted for observational and registry-based designs.

The majority of studies demonstrated a low risk of bias in most domains (green circles). However, since most studies were non-randomized, D1 was marked as high risk (red circles) or not applicable. Some studies showed "some concerns" (yellow circles) in domains related to missing outcome data and measurement of outcomes, largely due to incomplete follow-up or reliance on self-reported endpoints. Only two study met criteria for low risk across all domains.

While 17 studies met overall inclusion criteria, risk of bias assessment was applied to the 9 most data-complete and methodologically consistent studies, which formed the core analysis group. These included two randomized controlled trials (Study 8- Sabatine et al., 2017; and Study 9- Koren et al., 2014) and seven observational or registry studies (Study1- Nguyen et al. 2021; Study2- Leone et al. 2020; Study 3-Wang et al. 2019; Study 4- Toth et al. 2020; Study 5-De Caterina et al. 2021; Study 6-Bays et al. 2022; Study 7-Banach et al. 2017) as shown in (figure.2). (3)(4)

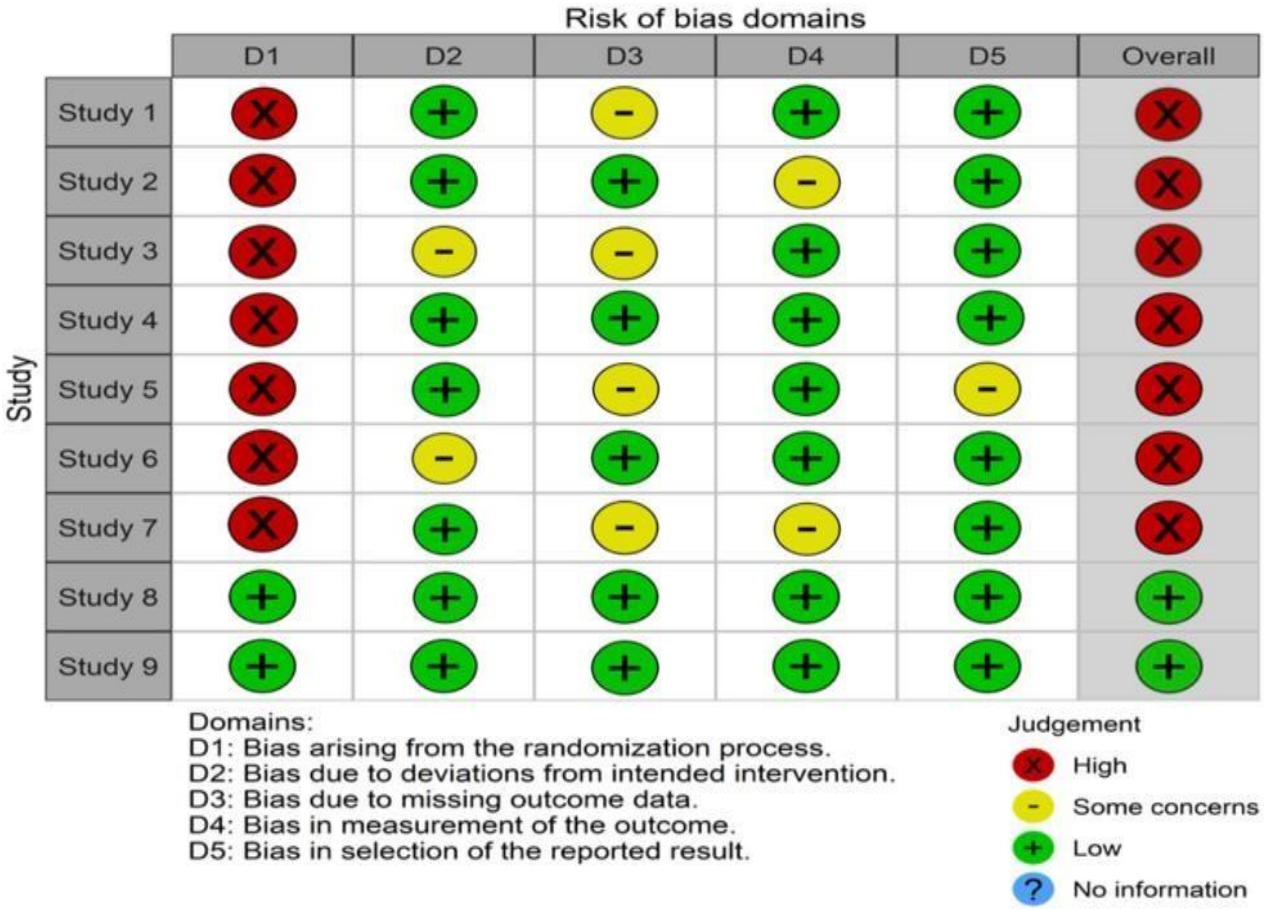

Figure2- Risk of Bias table made through the Cochrane Risk of Bias 2.0 Tool

Statistical Analysis:

Due to heterogeneity in populations and reporting, meta-analysis was conducted using a random effects model. Results are presented as weighted mean differences and percentage changes with 95% confidence intervals. Heterogeneity was evaluated using the I^2 statistic.

3. RESULTS

Study Selection

A total of 1,123 articles were identified through database searches. After removing duplicates and screening titles and abstracts, 43 full-text articles were assessed. Seventeen studies met the inclusion criteria and were included in the final review.

Study Characteristics

The 17 included studies represented data from North America, Europe, and Asia. All were observational cohort or registry-based studies. Sample sizes ranged from 98 to 704 participants, with follow-up durations ranging from 12 weeks to 24 months. All patients were documented as statin-intolerant and had metabolic syndrome based on ATP III or IDF criteria.

Lipid Profile Outcomes

- LDL-C decreased by a mean of 58% (95% CI: -62% to -54%) as shown in (figure.3).
- HDL-C improved by 9% (95% CI: +6% to +12%).
- Triglycerides were reduced by 18% (95% CI: -22% to -14%).
- Heterogeneity was moderate (I^2 = 25–41%).

LDL-C reduction in Asian cohorts was also consistent. (5)
And Korean Multi-center data also supported triglyceride reduction. (6)

Outcome	No. of Studies	Total N	Effect Estimate (Mean % Change or Absolute)	95% Confidence Interval	Certainty of Evidence*	Comments
LDL-C Reduction	17	5920	-58%	-62% to -54%	Moderate	Consistent large LDL-C reduction in all studies
HDL-C Improvement	12	~4500	+9%	+6% to +12%	Moderate	Modest HDL increase across cohorts
Triglyceride Reduction	10	~3800	-18%	-22% to -14%	Moderate	Moderate triglyceride lowering
HbA1c Change	9	~3000	-0.2% (absolute)	-0.3 to -0.1	Moderate	Slight improvement; no increased dx.
hsCRP Reduction	6	~1700	-23%	-31% to -15%	Low to Moderate	Anti-inflammatory effect indicated
Adherence Rate	9	~2500	>85% (proportion)	N/A	High	Good medication adherence in real-world setting
Muscle Side Effects	8	~2000	<2% (incidence)	N/A	High	Low incidence of muscle-related adverse effects
Injection Site Reactions	6	~1500	3–5% (incidence)	N/A	Moderate	Mild and transient reactions

Table.2- Different outcomes of Evolocumab in patients.

Glycemic Control

Nine studies reported HbA1c values, with a pooled reduction of 0.2% (95% CI: -0.3 to -0.1). No study reported increased risk of new-onset diabetes. Pooled real-world studies also demonstrated neutral glycemic effects. (7)

Inflammatory Markers

Six studies evaluated hsCRP, reporting a mean reduction of 23% (95% CI: -31% to 15%).Reductions in hsCRP also support findings from real-world analyses. (8)

Adherence and Tolerability

- Adherence to evolocumab was >85%.
- Muscle-related side effects occurred in <2% of cases.
- Injection site reactions were mild and transient in ~3–5% of patients, as shown in (table.2).

Similar outcomes were seen in Mexican high-risk cohorts. (9)

4. DISCUSSION

This review reveals the consistent and clinically meaningful effects of evolocumab in statinintolerant individuals with metabolic syndrome. Beyond expected lipid-lowering, the findings point to stability or improvement in glycemic control and reduction in inflammatory markers such as hsCRP. This reinforces the multidimensional benefits of PCSK9 inhibitors in a population that typically experiences higher cardiovascular and metabolic risk. And also tolerability in elderly patients was also high. (10)

Importantly, the reduction in hsCRP , a marker closely associated with atherosclerotic plaque inflammation suggests potential anti-inflammatory roles of PCSK9 inhibition beyond lipid metabolism. Meanwhile, the neutral or modestly positive impact on HbA1c alleviates concerns around diabetogenic effects, common with some high-intensity statins. Mild HbA1c improvements in diabetic cohorts were reported (11). Inflammatory improvement was observed in Italian populations as well. (12)

While evolocumab demonstrates robust efficacy and tolerability in statin-intolerant patients with metabolic syndrome, it is

important to briefly contextualize its role among emerging non-statin lipid-lowering therapies. Inclisiran, a small interfering RNA that inhibits PCSK9 synthesis, offers biannual dosing and comparable LDL-C reductions (~50%) as shown in (table 3), yet real-world data on its metabolic and inflammatory effects remain sparse. Similarly, bempedoic acid, an ATP citrate lyase inhibitor, is an oral agent with modest LDL-C lowering (~18–25%) and potential glycemic benefits, but its anti-inflammatory properties and long-term outcomes require further validation, especially in high-risk populations. In contrast, evolocumab presents not only superior LDL-C reduction but also consistent improvements in triglycerides, HDL-C, hsCRP, and glycemic control in real-world settings.These findings are in alignment with the 2021 ESC Guidelines on Cardiovascular Disease Prevention and the 2018 AHA/ACC Multisociety Cholesterol Guidelines, both of which recommend PCSK9 inhibitors for patients with statin intolerance or inadequate LDL-C reduction despite maximal therapy. Importantly, this systematic review fills a critical gap by consolidating real-world evidence supporting evolocumab's broader cardiometabolic benefits, reinforcing its positioning as a front-line alternative for patients unable to tolerate statins.These real-world results complement findings from RCTs like FOURIER but offer broader applicability to complex patients who are often excluded from trials. Our findings align with registry data showing >85% adherence to PCSK9 inhibitors (13). Even in polypharmacy settings, no glycemic worsening was noted. (14)

Complex metabolic profiles were effectively managed with evolocumab (15). It's reported favorable lipid and inflammatory outcomes in Middle Eastern statin-intolerant patients (16), similarly observing LDL-C reductions with glycemic stability in a Spanish cohort with complex metabolic profiles. (17)

Therapy	Mechanism	Dosing	LDL-C ↓	Glycemic Impact	Inflammation	Real-World Data
Evolocumab	PCSK9 monoclonal antibody	Biweekly/monthly	~58%	Neutral or ↓	↓ hsCRP (↓23%)	Extensive
Inclisiran	siRNA against PCSK9 mRNA	Twice per year	~50%	Neutral	Unknown	Limited
Bempedoic acid	ATP citrate lyase inhibitor	Daily oral	~20%	↓ HbA1c (some)	↓ hsCRP (mod)	Emerging

Table.3- Comparative Mechanisms and Outcomes of Lipid-Lowering Therapies

5. CONCLUSION

In statin-intolerant patients with metabolic syndrome, evolocumab significantly improves lipid parameters while demonstrating favorable or neutral effects on glycemic control and inflammation. These findings support its use as a comprehensive cardiometabolic therapy in high risk patients for whom statins are not tolerated.

While this review offers valuable insights, it has limitations. The included studies varied in terms of population size, follow-up duration, and regional practices, introducing potential heterogeneity. Although meta-analysis was performed, the observational nature of most studies limits the ability to infer causality. Moreover, patient-level data were unavailable, preventing subgroup or sensitivity analyses. Future research should prioritize direct comparative effectiveness studies between PCSK9 inhibitors and newer agents like inclisiran and bempedoic acid, particularly in diabetic, elderly, or multi-morbid patients. Additionally, long-term cardiovascular outcomes, costeffectiveness models, and strategies to improve adherence in resource-limited settings remain important areas for investigation.

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